



# Basic Symptom Control in Paediatric Palliative Care

together  
for short  
lives 

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Formulary

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## Foreword

The Basic Symptom Control Manual, now in its 10<sup>th</sup> edition, has been a mainstay in caring for children with palliative care needs since its first publication in 1997.

It is put together by doctors and nurses experienced in the field and captures their knowledge from being 'at the bedside' of children with pain and a variety of complex symptoms. In a field where robust evidence is often lacking, this Manual provides an invaluable tool to support professionals across the globe when caring for children with conditions and symptoms which may be unfamiliar or uncommon in their routine practice. The difference that access to this simple resource can make to the confidence of clinicians and hence the comfort of the children in their care is immeasurable.

With 33 chapters ranging from Anorexia to Tracheostomy care, the Manual includes information on assessment, causes and management of symptoms, with references provided where these exist. At the back of the Manual, you will find the Children's Palliative Care Formulary, published by the Association of Paediatric Palliative Medicine (APPM) on which this resource is based.

We know that research needs to catch up with rapidly developing practice, to keep pace with the growing number of babies, children and young people live longer with increasingly complex health needs. The teams that put together the UK's [NICE Guideline on End of Life Care for Infants, Children and Young People](#) and the recent [WHO Guidelines on the Management of Chronic Pain in Children](#) both raised this as an urgent need if we are to develop the field of paediatric palliative care. This is something being addressed by the APPM and I look forward to the publication of their three clinical guidelines.

I would like to thank the authors who have given their time to write chapters and share their knowledge freely. But most of all I want to acknowledge Dr Sat Jassal, without whose commitment and passion over the past 25 years this Manual would not have seen the light of day.

Whether you are providing care in a developed or developing country I hope it will provide you with reassurance that you are following the best practice possible, even if your resources and access to medications and equipment may be limited.

Together for Short Lives is delighted to publish this manual and make it freely available.



Dr Hilary Cass OBE  
Outgoing Chair Board Trustees, Together for Short Lives

## Introduction

**This edition has been updated to the latest edition of the APPM Formulary 6<sup>th</sup> Edition 2024. The contents of the symptom management remain unchanged.**

Welcome to the 10<sup>th</sup> edition of the Together for Short Lives Symptom Control Manual. This manual has been written to allow doctors and nursing staffs in hospitals and in the community an understanding of the basis of Symptom Control in Paediatric Palliative Care.

This manual 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.

Almost all of the chapters have been extensively rewritten (with some new chapters) by some of the most experienced doctors and nurses in the field in the UK. A big thank you must go out to all of them for their hard work and generosity in sharing their knowledge and time.

The formulary has been adopted from the latest Association of Paediatric Palliative Medicine Master Formulary. There are over 850 references in the Manual. We have put the references at the back so those who wish to have a lighter version can avoid printing them.

There is much more to supporting the terminally ill child and family than just the symptom control outlined in this manual. We must remember the important emotional, social and spiritual needs of the child, siblings, parents, grandparents, family and society around the child.

We teach new workers in the speciality 3 basic first rules: -

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 child, parents and team around the child.

The second rule is to document and disseminate information to all of your care team. Check that they are happy about the care plan and that everyone is clear about their role.

The third rule is beware that you do not fall into the same trap as Icarus (who flew too close to the sun). 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 must look after. Remember to retain a sensitive professional distance.

This manual is provided free of charge and all the contributors have worked on this Manual voluntarily 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 translate or use the work in a specific way then contact me for approval; I rarely say no.

Dr Satbir Jassal

# Anorexia

[1-8]

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 these different possible causes and involving a dietician. It is also, 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, eg fast food, are 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 & Urology

[9]

The bladder, as with all other organs, may cause symptoms towards the end of life – sometimes the symptoms may occur in isolation but also, they may occur in tandem or fluctuate between each other:

- Incontinence
- Spasm/ bladder instability
- Retention

**Incontinence** may be long standing as part of a child's underlying condition or may be a new symptom caused by altered neurological function, lack of consciousness/ awareness or drug side effects. It is also important to exclude an acute cause such as urinary tract infection or constipation, which may be treatable. Loss of bladder function may cause great distress to both the child and their parents/carers. The use of pads is non-invasive and simple, although may require a careful approach of tact and sensitivity to introduce.

**Spasm** may also be a long-standing symptom that deteriorates, or a new symptom towards end of life. It may cause pain or discomfort but also may result in altered micturition with frequency, leakage or urge incontinence.

Spasm may be caused by constipation, anxiety, use of stimulants and other medications, bladder stones, catheter irritation or neurological conditions.

Management should include targeting the cause where possible or may require medications such as Oxybutynin hydrochloride (of note it can be administered enterally or intravesicularly).

**Retention** may be caused by outflow obstruction from the bladder (e.g. by stones or tumour), medications (such as opiates), neurological issues impacting on nerve supply to bladder (underlying neurological disease or dysfunction at end of life) or infections. 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. Gentle bladder massage, warm baths or catheterisation may help alleviate an obstruction.

Catheters may be used for management of retention or for incontinence (if it is causing significant distress or proving difficult to manage). Catheters may be indwelling or used intermittently (dependent on clinical situation and availability of persons able to insert catheters).

Catheters are measured in French (Fr) which defines the external diameter of the tube. To minimise trauma, use the smallest size that will still allow sufficient drainage. Catheters will have balloons that should be inflated using sterile water. Catheter bags should be kept below the level of the bladder to promote good drainage. If output reduces or stops despite no change to fluid intake – check for tube displacement, kinking or blockage. If the catheter is blocked it may need a wash out or the use of a catheter patency solution.

The monitoring of urine output may provide an indicator of underlying health status but cannot and should not be used to predict imminence of death.

## Bleeding

Bleeding could be a recurrent or troublesome symptom in children and young people in palliative and end-of-life care situations.

### Common causes

- malignancies – haematological malignancies, solid tumours with bone marrow infiltration
- thrombocytopenia due to chemotherapy
- secondary to radiotherapy
- liver diseases
- other conditions causing disseminated intravascular coagulation or coagulopathy.

### Management

Should be individualised and should depend on the cause, the amount and type of bleeding, the stage of disease and the prognosis and goals of the patient and family at the time.

- Platelet and/or other blood-product transfusions may be appropriate to treat or prevent bleeding in patients who are not in the very terminal phase.
- Liver dysfunction with coagulation abnormalities may be helped with Vitamin K both orally (prevention) or by injection (acute bleed).
- Gastro-protection with proton-pump inhibitors and/or H2 blockers should continue, if possible, when gastric bleeds are anticipated.
- Vaginal bleeding may respond to oral progestogen. (Avoid sudden withdrawal of progestogen in young women who have been on them previously).
- Small soft tissue bleeds may be dealt with by using pressure bandages, topical Adrenaline 1:1000 on a gauze applied directly to the wound and oral tranexamic acid.
- Bleeding gums may be helped with tranexamic acid mouthwashes and/or absorbable haemostatic agents such as Gelfoam or Gelfilm.

**Massive/ terminal haemorrhage** is uncommon in children, even in those with leukaemias. In adults these are usually arterial bleeds from tumour invasion of major arteries. Nevertheless, as the sight of blood could be very distressing to patients and carers, a gentle warning of the possibility might be appropriate depending on the situation. This could help prepare the family for such an event and help avoid inappropriate emergency measures in a patient who is dying.

In the unlikely event of a catastrophic haemorrhage, the family should be reassured that it is not causing pain to the child or young person. If the patient is conscious and distressed by the sight of blood, sedation with buccal midazolam and diamorphine, followed by intravenous (if access available) or sub-cutaneous infusions may be appropriate. It is important to emphasise that although respiratory depression may be a side effect of such treatment, hastening death is not the intention.

If massive haemorrhage is anticipated, the use of dark-coloured towels and bedding may help reduce the visual impact of blood.

# Cough

[2, 10-21]

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 secretions particularly in 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 nebulisers 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 several conditions, particularly neurodegenerative disorders, the loss of the ability to cough is a major problem. Good physiotherapy, postural 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.



## Constipation

[22-39]

Constipation is a common condition affecting up to a third of all children and thought to occur even more frequently in those who are tube fed. It is recognized as a very common symptom during palliation and at the end of life, occurring in 40-50% of children.

### Contributing risk factors to constipation

Constipation in the palliative care setting is most often multimodal in origin, requiring a combination of interventions to relieve both constipation and the associated symptoms.

- **Hydration and diet:** Reduction in fibre and fluids may affect gut motility
- **Medication**
  - Opiate Induced Constipation (OIC) - Well recognised, particularly in the end-of-life phase with escalation of opiates
  - Other medication - For example anticholinergics (Hyoscine), Ondansetron, Amitriptyline
- **Need for NG/NJ tube:** Children with a G/J tube have a higher total number of symptoms including constipation.
- **Neurological:** Children with severe impairment of the central nervous system experience gastrointestinal symptoms at a high rate and severity. The gut-brain connection is impaired, manifesting in various symptoms including constipation that requires a fine balance of pain management, bearable medication side effects and feed tolerance.
- **Inactivity/immobility:** As a child's health deteriorates then their mobility and activity levels can reduce contributing to constipation. Children with progressive, non-curable conditions who require extensive mobility modifications are associated with higher numbers of symptoms including constipation.
- **Electrolyte imbalance:** For example, hypercalcaemia and hypokalaemia.
- **Pain and discomfort:** a child experiencing pain or discomfort from various causes may avoid mobilizing to the toilet or straining whilst on the toilet, worsening the constipation cycle.

### Investigations

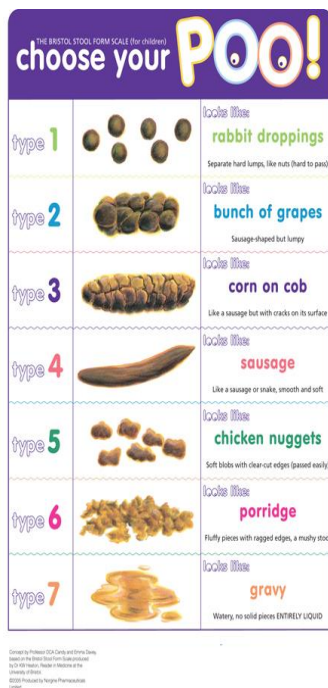
- The use of a plain abdominal radiograph or ultrasound to make a diagnosis of constipation is not recommended in palliative care due to poor correlation between observers, reported symptoms and colon transit times. It may be considered if requested by specialist services in the ongoing management of intractable constipation or concerns about other diagnoses.
- Investigation and referrals to other services may be appropriate in refractory constipation for consideration of uncommon complications.

## Signs and symptoms of constipation

- Not opened bowels at least 3 times in the last week
- Stool is large and hard
- Stool looks like “rabbit droppings” or little pellets
- Straining or pain when opening bowels
- Bleeding during or after having bowels opened
- Poor appetite or stomach pain that improves after having bowels opened
- Lack of energy, irritable or have a poor sleep pattern
- Lots of wind which may be foul smelling
- Overflow diarrhoea: this is loose, often offensive smelling stool, which leaks out around hard, constipated stool.

## The Bristol Stool Chart

The Bristol Stool Chart helps describe a child’s stools. Stools are graded according to their hardness with type 1 stools being the hardest and type 7 stools the loosest.



## Management of constipation

In the palliative care setting a combination of non-pharmacological approaches and medication is used to treat constipation and alleviate the symptoms experienced.

### Non-pharmacological interventions

*Diet:* Increase in fibre and fluid, as tolerated. A dietician may be helpful in adjusting a child's feed and fluid regime in a tube and supplement fed child.

*Heat:* Applying a heat pack to the abdomen may reduce the pain experienced with constipation.

*Mobility:* Increased physical activity or regular changes in position including more time in a standing frame or a chair.

*Abdominal massage:* Abdominal massage has been shown to improve quality of life, reduce need for laxative medicines and improve the consistency and frequency of bowel movements in physically disabled children.

*Toileting:* Sitting on the toilet/commode is helpful in developing and supporting a regular bowel habit. When sitting on the toilet, a child's feet need to be supported to ensure their knees are higher than their hips.

### Pharmacological management

Review the child's medication(s): Identify those that may cause constipation and consider that some medications may combine the benefits of their intended prescription and offer side effects that improve gut motility, e.g. Erythromycin.

Medications commonly used to treat constipation in children and young people can be divided into 3 broad categories: Osmotic laxatives, stool softeners and stimulants.

### General approach

Step 1: Start with an osmotic laxative, Movicol first line, and increase dose if needed

Step 2: Add in a stimulant after a few days if necessary

Step 3: Add in sodium picosulfate or consider an enema

Step 4: Review compliance and laxative combinations

Explore with the child and their family the most tolerable combination of laxatives that supports good compliance, to ensure relief of constipation in a timely and effective manner. Often a combination and escalation of laxatives is needed. The use of enemas may be considered invasive, distressing, and intrusive in some cases whilst in others, a rapid effective intervention to relieve symptoms rapidly. The decision to use enemas should be offered and explored if oral intervention is increasingly burdensome or not offering rapidly effective results. When relief of constipation is achieved consider appropriate ongoing bowel management with regular laxatives.

As the child's condition changes, they may become more debilitated, and their oral intake (food and fluids) may change and reduce. The child's ability to tolerate medication, even in the presence of

gastrostomy or NG tube, may become burdensome and there may be challenges around absorption of feeds and medication, especially towards the end of life. Review of laxatives at this stage should focus on small volume tolerance with greatest benefit without causing further symptoms, e.g cramping abdominal pain due to stimulant laxatives.

## Laxative table

Type	Mechanism	Notes
<b>Osmotic laxatives:</b> (oral, NG or PEG only)	Increase the amount of water in the large bowel.	There are 2 different types of osmotic laxatives
Polyethylene glycol 3350 + electrolytes (Macrogols) eg Movicol or Laxido	Retains the fluid in the bowel which it was mixed and given with. Escalating doses can be given	Paediatric and Adult Movicol sachets available. Considered <u>first line</u> in managing constipation.
Lactulose	Draws fluid from the body into the bowel.	Useful as alternative to Movicol in: <ul style="list-style-type: none"> <li>• children who do not tolerate larger oral fluid volumes</li> <li>• neonates/infants with cardiac conditions</li> </ul>
<b>Stool softeners:</b> (oral, NG or PEG and rectal routes)	Work by helping fluid in the bowel to mix with stools to soften them	
Docusate Sodium (oral, NG or PEG route)	A surfactant laxative, increases water penetration into stool	Useful addition to Movicol to soften stool and ease defaecation
Arachis oil enema (rectal route)	Lubricates and soften the stool	Avoid in peanut allergy. Give in the evening to work overnight and follow with phosphate enema in the morning. In rare circumstances, give ½ dose arachis oil and ½ dose phosphate enema in one procedure where repeated enemas are not considered appropriate.
<b>Stimulant laxatives:</b>	Work by stimulating the muscles in the wall of the intestines, causing them to push the stool through more effectively.	May cause stomach cramps, particularly if there is hard stool in the bowel. Start with osmotic and

(oral and rectal routes)		softeners and then add in a stimulant if necessary.
Senna (oral route)	After metabolism of sennosides in the gut, the anthrone component stimulates peristalsis.	Add Senna, if needed, after a few days of an osmotic laxative to encourage the movement of the softened stool through the bowel.
Bisacodyl (oral or rectal route)	Works by stimulating enteric neurones to cause peristalsis and stimulation of intestinal secretions.	Bisacodyl can be given orally or rectally. It is particularly useful in its suppository form.
Sodium picosulfate (oral route)	Releases bound water from faeces and stimulates the mucosa thereby increasing the motility of the large intestine.	Add in if Movicol + senna/docusate sodium combination not effective.
Glycerine suppository (rectal route)	Acts as a lubricant and a mild irritant to evacuate the rectum of stool.	Comes in various sizes. Only empties rectum.
Phosphate enema (rectal route)	Osmotic activity increases the water content of the stool so that rectal distension follows allowing defecation by stimulating rectal motility.	Only use after osmotic or softener laxative have been given. Risk of phosphate absorption if enema retained.
Co-danthramer (oral route)	Works as a stimulant to encourage peristalsis.	Only for use in the palliative care setting due to long term carcinogenic effects. Very effective and tolerable due to small quantity and frequency needed.

## Disimpaction

The combination of history-taking and physical examination is used to diagnose faecal impaction by eliciting signs of overflow soiling and/or faecal mass palpable abdominally and/or rectally.

Follow disimpaction guidance which recommends escalating age-related dosing of Movicol, as the first-line treatment. Add a stimulant if the Movicol is not working. Consider adding docusate if the stools are hard. In some cases, enemas may be required; sodium citrate enemas (Fleet or Microlax enemas) can be offered. If this is not successful, then the use of phosphate +/- arachis oil enemas (check for peanut allergy) may be needed. After the disimpaction, a reduced dose of laxative should be given for several weeks to ensure a regular bowel habit.

## Opiate Induced Constipation (OIC)

Opiate induced constipation is a common symptom in palliative care. Review of the type of opiate may offer some reduction in side effects. For example, children may exhibit less constipation with use of transdermal fentanyl compared with other opioids.

Opiates inhibit propulsive gastrointestinal motility through the activation of gastrointestinal mu-opioid receptors. Clinical studies have demonstrated the safety and efficacy of peripherally acting mu-opioid receptor antagonists (PAMORAs) in alleviating constipation without diminishing the analgesic effect of opioid therapy. While laxative prophylaxis of constipation remains the first-line management option, PAMORAs are a recommended treatment option for OIC in adults. Naloxegol is recommended in NICE guidance as an option for treating adults whose constipation has not adequately responded to laxatives.

Diverse adult populations with OIC achieved best therapeutic response with the PAMORAs methylnaltrexone (oral or parenteral), naloxegol (oral only) and naldemidine (oral only), with a low risk of serious adverse events. In a real-world study, oral naloxegol taken daily was effective and well tolerated in adult cancer pain patients with OIC. Common side effects of PAMORAs include abdominal pain, flatulence, and nausea. They are contraindicated in bowel obstruction.

In paediatric palliative care, methylnaltrexone and naloxegol are both used clinically. In a small study, paediatric patients with critical illness had a bowel motion within 6 hours in 37% of cases (and 24 hours in 63% of cases) after their first dose of PAMORAs. No significant adverse events were observed. The study did not demonstrate any significant difference in efficacy between methylnaltrexone and naloxegol. Adolescents who received oral methylnaltrexone post-operatively had decreased length of stay, improved bowel function and use did not alter pain scale self-reporting or opioid consumption. Methylnaltrexone appears to be safe and efficacious in treating OIC in children and adolescents with progressive incurable cancer in both the inpatient and outpatient settings and with repeated dosing.

# Diarrhoea

[40-51]

Diarrhoea is a recognised symptom often reported by the child and their carers during palliation. It may occur in children as part of their underlying condition and management, or be due to an intercurrent illness, general deterioration, or an emerging new medical condition. A detailed history and examination will elucidate most diagnoses and determine the need for and benefit of tailored investigations and management approach.

## Causes

- Infection e.g. viral or bacterial infections
- Constipation and faecal impaction with overflow
- Treatment related:
  - Drug induced
  - Radiation/chemotherapy
  - Graft versus Host Disease (GvHD)
- Diet and food allergies
- Malnutrition/malabsorption e.g. resulting in Zinc deficiency
- Anxiety and distress
- Incidental childhood conditions:
  - Coeliac disease
  - Toddler's diarrhoea
- Adolescent inflammatory bowel disease
- Gut specific:
  - Bile acid diarrhoea: excess bile acid (e.g. from ileal disease/dysfunction) in the colon causes diarrhoea through effects on electrolyte balance and speeding up of large bowel transit time
  - Small bowel bacterial overgrowth
  - Gut dystonia or autonomic neuropathy often related to disconnection between the brain and gut in some children with severe neurodisability
- Surgical causes (for example, small bowel resection, internal fistulae)

## Decision making regarding investigation and treatment

A general approach should be to consider the impact of the diarrhoea on the child and family, and whether investigations and treatment would provide meaningful benefit and improvement in symptoms experienced when balanced against the burden these strategies might entail.

The impact of severe chronic diarrhoea should not be overlooked since it can result in dehydration, electrolyte derangement and malnutrition (esp mineral and vitamin deficiencies). It may also cause more localized skin issues with soreness and excoriation around the nappy area.

## Management

### Initial assessment

*History* including bowel habit (acute/chronic), type of stool (frequency, consistency, colour, presence of blood, water content) and associated symptoms (e.g. nausea, vomiting and pain). If constipation and overflow are diagnosed, then it should be treated accordingly.

*Physical examination* of the gastrointestinal system including, where appropriate, the nappy area for signs of rash or excoriation, signs of dehydration and malnutrition.

*Stool sample:* consider if an infective cause is likely.

*Diet and food allergy review:* e.g. the consumption of excess fruit juice is often considered a contributor to Toddler's diarrhoea. A dietician's assessment would be beneficial. If a child has a potential food allergy, then referral to their local paediatrician is advised.

*Medication review:* many medications can cause diarrhoea including PPI, NSAIDs, laxatives, chemotherapy, and SSRI.

*Age-related childhood conditions:* chronic diarrhoea in children may be a new emerging condition which is often a complex age-specific disorder that requires an age-specific management.

### Treatments

*Oral Rehydration Salts (ORS)* remain the mainstay treatment for nearly all approaches to acute watery diarrhoea and dehydration. Different formulations, attempting to address sodium-glucose co-transportation to facilitate water absorption and other co-transporters have been explored. These solutions offer variable osmolality and electrolyte compositions targeting common and unique pathophysiology and have met with varying success. Fruit juice is not recommended since it can lead to hyponatraemia in the presence of diarrhoea.

*Dietician review* which may advise a change in feed to support improvement in nutrient absorption, supplements to support weight gain or addition of fibre to manage constipation.

*Zinc deficiency* is considered rare in middle and high-income countries but may potentially occur more commonly in the palliative care population if poor nutrition and absorption have been longstanding challenges. Zinc deficiency is associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function. Zinc supplementation has been found to reduce the duration and severity of diarrhoeal episodes in the developing world. Supplements are effective regardless of the type of common zinc salt (zinc sulphate, zinc acetate or zinc gluconate) used. High zinc intakes may compete for absorption with other micronutrients such as iron and calcium.

### Medication

*Antidiarrheal and antimotility agents* are not indicated or recommended in the treatment of infectious diarrhoea. Both Loperamide (Brand: Imodium) and Co-phenotrope (use in over 16 years only) can be used medically to control persistent diarrhoea.



*Incidental side effects of other symptom medication* may also provide a gut slowing (constipating) effect e.g. Ondanstreton (antiemetic), Buscopan (abdominal cramping) or Opiate (analgesic).

*Antibiotic associated diarrhoea:* Antibiotics can cause diarrhoea during and for a period after cessation of treatment. In most cases this can be tolerated for the duration of the antibiotic course, but in severe cases a change to the recommended antibiotic may be considered for future potential infections. The use of probiotics for preventing antibiotic associated diarrhoea in non-immunocompromised children can be guided by the presence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes. In these cases, *Lactobacillus rhamnosus GG* or *Saccharomyces boulardii* are both strongly recommended with moderate quality of evidence. In the case of preventing *Clostridium difficile*-associated diarrhoea, then *S. boulardii* may be of benefit (low quality of evidence, conditional recommendation). Other strains or combinations of strains have been tested, but sufficient evidence is still lacking.

## Dyspnoea

[52-58]

Dyspnoea is from the Greek words for 'difficult breathing'; the uncomfortable, subjective awareness of difficulty in breathing. It is a common symptom in both malignant and non-malignant palliative conditions, often contributing to a significant symptom burden [1]. However, as self-report is the only reliable measure, this is challenging in many younger or non-verbal children.

The sensation is derived from a complex interaction between respiratory function, perception of physical respiratory effort (with input from mechanoreceptors, chemoreceptors, and the medullary respiratory centre) with important contributions from psychological, social, and spiritual components. Dyspnoea is often frightening and distressing and can result in a cycle of anxiety and breathlessness, each exacerbating the other. Dyspnoea does not correlate with respiratory rate, oxygen saturations or blood gases.

### Assessment

Careful assessment is a priority to elucidate any contributing factors and potentially treatable causes. Questions to consider include:

Is there a background (chronic) breathlessness?

What is the speed of onset of dyspnoea?

Are there precipitating or relieving factors?

Is dyspnoea purely related to physical activity?

Is dyspnoea affected by position?

Is there diurnal variation? Is it worse at night?

Are there associated feelings of panic?

The extent of investigations should be carefully considered balancing the potential gains against the burdens. These may include oxygen saturation recordings, sleep studies, full blood count, blood gases, lung function, chest X-rays or echocardiograms. Assessment scales for evaluating severity exist, but these have generally not been validated for the paediatric palliative population and used more commonly for patients with cystic fibrosis or asthma.

### Causes

Increased effort to breathe may be caused by increased airway resistance or decreased compliance, muscle weakness or structural abnormalities. The mechanics of breathing in young babies is also altered by highly compliant ribcages. Other causes can increase ventilation requirements due to

metabolic acidosis, hypoxaemia, or anaemia. A patient may have an acute cause of breathlessness on a background of chronic dyspnoea.

Conditions which can cause dyspnoea are varied and include:

- Cystic fibrosis
- Pulmonary interstitial disease
- Congenital heart disease
- Heart failure
- Respiratory muscle dysfunction, e.g. neurodegeneration, myopathy
- Cerebral tumours, raised intracranial pressure

Other pathologies include:

- Anaemia
- Pleural effusion or pneumothorax
- Pain
- Scoliosis
- Ascites
- Hepatic or renal impairment
- Infection
- Metabolic acidosis
- Cough, haemoptysis
- External pressure on airways
- Fluid in airways
- Thoracic wall pathology
- Hypoxaemia
- Bronchospasm
- Anxiety, panic, fear, or claustrophobia

## Multi-dimensional Management

The aim of management should be to improve the patient's subjective sensation and quality of life. However, there should be clear, realistic priorities and goal setting can be useful. Symptom management can take place alongside any treatment directed at the cause. Treatment directed at a cause of dyspnoea must be carefully weighed up between the clinical team, family, and child (where possible and appropriate). Interventions such as blood transfusions, chest drains and ventilatory support have varying burdens and benefits. The longevity of any potential benefit gained is an important factor. Through discussion, the most appropriate treatment decisions can be made jointly.

A combination of different modalities can be employed. These may include non-pharmacological management, disease orientated treatment, oxygen, opioids, and anxiolytics. As always in palliative care, regular, frequent reviews are essential as symptoms can escalate quickly.

## Non-pharmacological management

Optimising the climate around the child can bring considerable comfort. This may include keeping the room cool, adding humidity, and ensuring calm surroundings. Careful positioning can enhance respiratory mechanics and improve ventilation.

Viewing respiratory stamina as a limited currency, some children can participate together with their carers to plan and pace activities to minimise exertion and prioritise wishes. This can improve overall well-being and help to regain some sense of control over breathlessness. Cognitive therapy delivered by psychologists or play therapists may include learning relaxation and self-hypnosis techniques. Some children find acupuncture or acupressure beneficial.

Physiotherapists can offer a range of treatments, with appropriateness depending on the child's condition. These include breathing exercises to help strengthen respiratory muscle function or improve mechanics and secretion management techniques through postural drainage, percussion, or suction (see also chapter on secretion management).

The use of a hand-held fan can significantly reduce the sensation of dyspnoea, with evidence from adult trials [2]. It is an easy, non-invasive, and cheap intervention, bringing a sense of control to cognitively able children. The mechanism of this action is unclear, possibly involving the trigeminal nerve or nasal and oral mucosa receptors.

## Oxygen

Additional oxygen may be of benefit to children with specific conditions such as interstitial pulmonary disease, cystic fibrosis, or pulmonary hypertension. However, some children even with documented hypoxaemia do not gain any symptomatic benefit. Additionally, caution should be exercised in children with potentially raised carbon dioxide levels who may be reliant on a hypoxic respiratory drive. Adult studies show variable benefits to additional oxygen administration compared to air given in a similar route [3].

Often careful counselling of families away from monitoring saturations is needed, with a focus instead on addressing symptoms and optimising quality of life. One option may be to provide a trial of oxygen but discontinue it if there is no perceived symptomatic benefit. Safety is paramount to having oxygen in the home with an environmental assessment required before prescription. This is done in liaison with the local Home Oxygen Assessment service or local Home Oxygen Supplier. Ordering requires a home oxygen consent form, Initial Home Oxygen Risk Mitigation Form (IHORM) and Home Oxygen Order Form (HOOF). Oxygen can be administered from cylinders or a concentrator depending on the rate and circumstances.

## Opioids

Use of medications in palliative children is extrapolated from adult studies. Oral or subcutaneous opioids in lower doses than for pain are effective in reducing dyspnoea in adult patients. Nebulised opioids were not as effective as systemically administered opioids [4]. It is proposed that this action may be through the reduction in responsiveness of brainstem respiratory centres, thereby reducing the perception and sensation of breathlessness. They may also act by decreasing oxygen consumption, reducing sensitivity to high carbon dioxide and/or improving cardiovascular function. The reduced symptom burden can have a significant effect on improving psychological distress.

It is most common in paediatric practice to prescribe opioids at 25-50% of the analgesic dose (in opioid naïve children). In adults, on established opioids for pain management, an increment of 25% is sufficient to relieve dyspnoea. A comparable step can also be made for similar children on established opioids. In a parallel with pain management, once the opioid need is ascertained with short-acting medications, conversion to a long-acting form can be beneficial not just with ease of administration, but also providing smoother pharmacokinetics and improved symptom relief. The availability and use of additional short acting opioid doses for breakthrough dyspnoea can be helpful.

## Anxiolytics

Given the interplay between anxiety and dyspnoea, a potential role for anxiolytics could be surmised, however, a review for benzodiazepines for the relief of breathlessness in advanced disease in adults did not show positive or negative evidence for use compared to placebo. Drowsiness and somnolence were the main side effects noted [5].

One adult study used midazolam as an adjunct to morphine for dyspnoea relief to good effect [6]. A benzodiazepine could therefore be considered and trialled on an individual basis, particularly where anxiety is especially troublesome (in addition to opioid prescription). Anticipatory consideration of a fast-acting benzodiazepine may be useful if there is the possibility of a severe, acute dyspnoeic event (such as severe pulmonary haemorrhage).

## Summary

Dyspnoea is a common symptom in paediatric palliative care. Treatment of the underlying cause should be carefully considered. Management should be multimodal, optimising the environment, using a hand-held fan and opioids in combination as first line. On an individual basis, trials may be considered of oxygen or anxiolytics. Addressing the psychosocial aspect of dyspnoea is effective and can be empowering for children who are able to participate.

## Emergencies in paediatric palliative care

[59-69]

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

### Types of emergencies in paediatric palliative care

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

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.

Anticipate what medication and doses may be needed and ensure appropriate drugs are 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 reversible?

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? Is the treatment likely to be more beneficial than burdensome.?

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, will the benefit be worth the move?

What are the child and family's priorities?

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 analgesics are used. Even with good early pain management, rapidly escalating pain and pain crises cannot always be avoided and must be managed as an emergency.

Points to consider:

- Are the current medications the right ones?
- If on an opiate, should there be a switch to an alternative opiate?
- If not on a neuropathic agent, does a neuropathic agent need to be added?

To get control of rapidly escalating pain, the best approach is to rapidly titrate medication according to response, whilst carefully monitoring for toxicity.

The ideal approach is often to set up intravenous or subcutaneous Patient Controlled Analgesia (PCA) so the patient can bolus the dose according to requirement. If the patient is unable to do

this, Patient-Proxy Controlled Analgesia (PPCA) or Nurse Controlled Analgesia (NCA) are acceptable alternatives. The pump can be set up to deliver continuous background analgesia and bolus doses, or just bolus doses.

Rapid titration of morphine or oxycodone:

When setting up a PCA, PPCA or NCA a general guideline is:

- Calculate the total daily background needed and hourly dose to be delivered
- Give bolus doses of 50% of the hourly dose
- If using PCA, set the pump to deliver a bolus every 5-10 minutes
- If using PPCA or NCA, set the pump to deliver a bolus every 20 minutes, although you may reduce this to 5 minutes depending on the clinical situation

If unable to access appropriate equipment to run a PCA, PPCA or NCA, an alternative approach is:

- Give 10-20% of the total daily opioid dose as a bolus, every 10-15 minutes
- Increase the bolus by 30-50% every third dose until effective analgesia achieved. This will now be the bolus dose you provide.

## Neuropathic pain

Neuropathic pain should always be considered when a patient has rapidly escalating pain despite opioids. It is particularly likely in patients with solid tumours.

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: If on an opioid, rotating to methadone may facilitate better neuropathic cover.
- Ketamine: sublingual or by continuous intravenous or subcutaneous infusion. Ketamine can also be added to a PCA, PPCA or NCA pump.
- Lidocaine patches: particularly if there is a localised focus of pain
- 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 is 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:**

This can occur as a terminal event. The goal of care is to get the child settled and comfortable as quickly as possible.

- Maintain a calm environment. Help the child find the optimal position, use a small fan to blow air gently across their face, implement any relaxation or breathing techniques they may be familiar with.
- Usually best management is achieved with a combination of morphine plus midazolam. Many of these patients will already be on morphine, so may only need midazolam added.

- Set up a PCA, PPCA or NCA giving a continuous infusion of morphine plus midazolam with bolus function. As a guide, a safe starting dose for midazolam is 5-10mcg/kg/hr background with a 5mcg/kg bolus every 5 minutes. The morphine dose should be calculated according to the child's current requirement. If not on a background opiate, a safe starting dose of morphine would be 5-10mcg/kg/hr background with a 5mcg/kg bolus every 5 minutes.
- An alternative option to PCA, PPCA or NCA is to commence a background infusion of midazolam 5-10mcg/kg/hr and give iv or sc bolus doses of midazolam as needed (see formulary for doses). This should be combined with a background opiate, based on the child's existing requirement.
- For children without iv or sc access, eg if an emergency occurs in the home with no professionals present, both Midazolam and Morphine can be given via the buccal route as needed (see formulary for doses).
- If pulmonary oedema is likely to be a contributing factor to the breathlessness, consider adding Furosemide via any route, including as a 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 with steroids, usually Dexamethasone (see formulary).

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 (see formulary).

Radiotherapy and/or chemotherapy may then be considered.

Spinal surgery may also be an option for some children.

Pain management will usually require both an opiate and a neuropathic agent.

## 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 benzodiazepines, such as midazolam, lorazepam or clonazepam. The route of administration will depend on the setting, but buccal and sublingual routes can ensure fast delivery at home.

It may be helpful to use an antipsychotic, such as haloperidol or olanzepine, in addition to (or in place of) a benzodiazepine.

Escalation of benzodiazepines can be associated with paradoxical agitation and we would not recommend rapid escalation of benzodiazepines without the use of an antipsychotic.

## Acute pulmonary haemorrhage

Acute pulmonary haemorrhage can be a dramatic and catastrophic terminal event.

Families must be warned if this is a risk.

Use dark coloured towels and bedding, so the visual bleeding is less dramatic.

Give buccal, intranasal, subcutaneous or intravenous Midazolam, repeating the dose until the child is settled (see formulary).

As soon as possible, and where available, set up a PCA, PPCA or NCA to deliver bolus doses of buccal midazolam, with a lock out set at a maximum of 5 mins (but could be as low as 1 min). A suggested starting dose is Midazolam 5mcg/kg.

Consider a continuous infusion of midazolam alongside bolus doses (see formulary).

## 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. Treatment will depend on the underlying diagnosis, current seizure management medication and previous responses to acute management.

All children at risk of seizures should have an emergency plan, which usually includes buccal midazolam (or rectal diazepam) and may also include paraldehyde.

If these are not effective, consider enteral, subcutaneous or intravenous half or full loading doses of eg phenobarbitone, phenytoin or levetiracetam. The choice will depend on the child's current seizure management medication. The dose may be dependent on the setting (eg home v hospital) and on past experience of the child's response, as well as current doses or information about recent drug levels (if available)

If seizures continue, medication may need to be delivered by continuous subcutaneous or intravenous infusion. Sometimes, switching the child's usual medication to a parenteral route will suffice. Sometimes a dose increase, or different medication is needed. Doses can be incremented until seizure control is achieved (see formulary for starting doses and advice re incrementation)

For children with severe neurological disorders who have been on multiple anticonvulsants, we have found a Midazolam infusion 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.

## Malignant bowel obstruction

Bowel obstruction is most common in children with pelvic and abdominal tumours.

Signs include:

- Nausea and vomiting. Vomiting can be persistent and can be bilious and, later, faeculant
- Cessation of bowel movements, sometimes with some 'overflow' diarrhoea initially, especially if on laxatives
- Abdominal pain and cramping
- Distended abdomen

It is essential to identify a potentially treatable underlying cause. For example, radiotherapy, chemotherapy or tumour resection may be an option. For some patients, a defunctioning ileostomy or colostomy may be appropriate.

- Symptomatic management with triple therapy is needed: analgesic, anti-emetic and anti-secretory medication.
- Octreotide reduces intestinal secretions and can be given by continuous intravenous or subcutaneous infusion (see formulary).
- Anti-emetics should be optimised, although in mechanical obstruction they may not have much obvious benefit. Prokinetic anti-emetics should not be used in complete bowel obstruction.
- Analgesia should be optimised. Anticholinergic e.g. Buscopan, can be a helpful addition.
- A nasogastric tube on free drainage or with gentle suction can reduce vomiting, although may not be needed if octreotide and anti-emetics are effective. The child should be kept nil by mouth unless they prefer to eat/drink and vomit. If they choose this option, they should only take small amounts.

## End of life care

[70-83]

***“If we don’t actually use the words dying, dead and death, people don’t always understand that that’s what we’re talking about...you’ve got to say the words.”***

Dr Kathryn Mannix, 2018

Delivering quality end of life care in paediatrics can (understandably) seem overwhelming. As ever, good communication is at the heart of providing good care alongside careful assessment and symptom management. There is only one chance to get it right so where possible death should be planned for (much in the same way as a birth). It should be possible for all healthcare teams to deliver this care with support, if and when needed from specialist paediatric palliative care.

A clinician’s role here is in enabling and facilitating the CYP (Child or Young Person) to have a ‘good death’. In paediatrics, this may be considered a contradiction in terms. However, research suggests that this can be defined as one in which *“the dying child receives optimal clinical care from a compassionate, respectful, and communicative multidisciplinary staff, and patient and family situational and psychosocial-spiritual needs are identified and met”*. Although this specific research was based on CYP in an intensive care setting, the principles apply to other locations. These aspects play into the bereavement experience of the family.

The other chapters in this book will provide a comprehensive overview of targeted symptom management. This chapter endeavours to focus on considerations around end-of-life care and the basics of symptom management in the last few hours to days.

### Prognosis

The hardest and most important question that CYP/families want to know the answer to – how long will the CYP live? This can seem like an almost impossible question. The key is providing an honest answer – this may be “we don’t know”, but in some cases of conditions associated with gradual decline, we may be able to provide some prediction.

Twycross has a caveat that can be useful for patients dying of cancer: *“If deteriorating month by month, the prognosis is likely to be months. If deteriorating week by week, the prognosis is likely to be weeks. If deteriorating day by day, the prognosis is likely to be days.”*

However, this is not an exact science and an infection, or palliative chemotherapy may further shorten or lengthen life against prediction. And for non-malignant conditions, it may be even more difficult to predict with waxing and waning periods. There may be periods of intensive treatment

where a CYP may succumb to their illness or may recover and return to their baseline or somewhere in between. This is where providing an opportunity to plan prior to the event can support the CYP to make the right, informed decision, or empower families to advocate for their CYP. We call this **Advance Care Planning** (not advanced!). This is not a one-off event, but a flexible and evolving process of discussion and documentation. This is typically best done by a health professional who knows the CYP/family well. It may be a specialist in paediatric palliative care, but certainly does not have to be, and may be better done by another health professional who leads on the CYP's care and knows them best. Most services will use a template to guide the documentation of these discussions, and the CYP/family (and others involved in CYP's care) will hold the completed document. Goals of care may move at different points in the child's condition, so this does not eliminate the need to revisit some of these conversations, but provides a background.

There will be some CYP/families who have been told multiple times that they are unlikely to recover, only to improve and return to a previous level of function. This 'boy who cried wolf' situation can lead to a breakdown in the health professional-family relationship. Having a compassionate and honest foundation with the CYP/family is key here. CYP/families respond well to health professionals vocalising uncertainty where this exists.

Signs of impending death will vary greatly based on underlying disease process, but the following may be signs that a CYP is reaching end of life:

- lack of energy
- drowsiness
- skin changes
- irritability
- pain
- oedema of the extremities

## Place of care

Much is written about preferred place of care whilst dying and in the UK, there is an assumption that given the choice, home is preferable. However, the *"opportunity to plan LOD [location of death] may be a better proxy for high quality end-of-life care than the actual LOD, one that is more inclusive, and better aligned with palliative care principles"*. It has further been stated that *"the proportion of seriously ill children who die at home or who attain a preference for place of death is not a useful outcome measure; neither reliably reflects the success of a team or of a system to provide quality healthcare or a good death"*.

Choice will be partly influenced by mode of death, and local service support. It is important to prepare the CYP/family for the possibility that their preferred choice may not be possible in some cases. However, facilitating care in the preferred place should be aimed for where possible. Intensive care units may be able to transfer ventilated patients to their preferred place of care for out of



hospital extubation and this could take place at the CYP's home, or local hospice or hospital, or another location.

Having support from local community teams is essential when supporting a child receiving end-of-life care at home. Children's community nurses and general practitioners (GPs) will often be key players in supporting both the CYP and the family, sometimes alongside local paediatricians. Advances in acceptability of virtual technology has allowed for more comprehensive support even to particularly rural areas (subject to internet connection).

Local hospices can also be an excellent choice for some CYP and families where they can be supported with experienced healthcare professionals in a dedicated environment.

Hospital remains the most common place of death for children with life-limiting conditions. It may be entirely appropriate and the right thing for the CYP/family to receive end-of-life care in the hospital, on a ward or even in the intensive care unit.

Early discussions regarding organ and tissue donation can be helpful in informing choice and these conversations may occur as part of the advance care planning process. If discussing as part of this, it is important that families understand what may be realistic. For example, organ donation is very unlikely to be possible where a child dies outside of the intensive care setting. However, tissue donation (e.g. eyes, heart valves, tendons, bones, skin) may be able to be obtained after death (typically within 24-48 hours) and therefore place of death can be more flexible with this in mind. Many hospitals will have 'Specialist Nurses in Organ Donation' (SNODs) who are experts in talking with families and healthcare teams about possibilities and early referral can be key here. They can also offer advice in advance about what may be possible on a theoretical basis, considering the child's underlying condition and comorbidities.

The importance lies in opening discussion about a CYP/family's priorities and options. It may be necessary to discuss and complete a 'do not attempt cardiopulmonary resuscitation' (DNACPR) form as part of the Advance Care Plan discussions, or at a later time. These should always be discussed prior to completion with the CYP and/or family.

## Communication and collusion

As suggested throughout this chapter, communication is perhaps the most important element in contributing to a 'good death'. There are many toolkits available to guide preparation and discussion for breaking bad news but SPIKES appears to be the most widely known and provides a useful template:

S – SETTING UP the interview

P – Assessing the patient's PERCEPTION

I – Obtaining the patients INVITATION

K – Giving KNOWLEDGE and information to the patient

E – Addressing the patient’s EMOTIONS with empathic responses

S – STRATEGY and SUMMARY

More recently, further research has focused on what parents consider to be the barriers to the breaking of bad news:

1. *a lack of (timely) communication*
2. *physicians’ failure to ask parents for input*
3. *parents feel unprepared during and after the conversation*
4. *a lack of clarity about future treatment*
5. *physicians’ failure to voice uncertainties*
6. *physicians’ failure to schedule follow-up conversations*
7. *presence of too many or unknown healthcare professionals*
8. *parental concerns in breaking bad news to children*
9. *managing indications of bad news in non-conversational contexts*
10. *parents’ misunderstanding of medical terminology.*

Utilising the SPIKES toolkit and considering strategies to avoid barriers to breaking bad news will stand you in good stead to build a strong doctor-patient relationship.

Parents may be concerned about how to break bad news to CYP, and this can lead to additional challenges around collusion. Collusion is the term used to describe when people (families and/or health professionals and others) may cooperate to deceive the CYP by withholding or not sharing information. This is often done with good intentions to protect an individual from the reality of the situation. However, it also results in the CYP being unable to make informed decisions about their treatment, being unable to plan for the future they have or the death they would like. It may also lead to a breakdown in relationships where the CYP may guess the diagnosis/prognosis and recognise there is some deceit. Evidence highlights that honesty and open communication is valued by CYP and research suggests that “sensitive, timely, age-appropriate information helps the dying child”. As health professionals, we should support parents in having open communication with their child and offer to facilitate this where possible.

Nevertheless, it is recognised that these conversations need to be well considered with regards to the information given and timing, as well as considering the developmental awareness of the CYP. There is increased recognition about the importance of explaining the process of what happens when someone dies. This can reduce fear and anxiety in both the CYP and the family when communicated compassionately and may be explained as part of an Advance Care Plan.

## Memory making (also known as legacy building) and wish charities

The family should be supported and encouraged to achieve any special wishes or goals they may have. There are many charitable organisations who can provide financial and emotional support for the CYP and their families at this time. It is important to have an awareness of some of these and particularly any charities local to you. In the UK, the charity Together for Short Lives is a good place to start. Some of these charities will grant a wish to a CYP and family and the chance to plan and enjoy this can be valuable in building memories e.g. a holiday away for the family in appropriate accommodation. During the end-of-life phase there may also be other opportunities for memory making e.g. hand moulds/prints, locks of hair, memory book, photography, art, writing, music, video. There is increasing evidence that these interventions may be associated with improvements in social, emotional, and spiritual variables for CYP and their families.

## Rationalising medications/interventions

In medicine we should always be weighing up the benefit and burdens of medications and interventions, but never more so than in the final days/weeks of a person's life. Make time to review the medications and medical interventions the CYP is undergoing regularly.

- Are there some 'non-essential' medications that could be stopped?  
E.g. Vitamins, medications for blood-pressure, or prophylactic antibiotics.
- Are there investigations that are no longer warranted?  
E.g. Blood tests, imaging etc. If no action will be taken based on the result of the investigation, it is most likely unnecessary and may be more distressing than not doing it.

This review needs to be personalised to the patient. For example, diuretics may continue to be useful to some patients in providing symptom management but for others the burden of additional medication may be too much.

In some cases, the need for a decision will be forced when a patient is no longer able to swallow oral medications, or their gut has slowed down to make enteral medication absorption limited. Consider, what can be converted to a different route, and what needs to be converted to a different route.

## Pre-emptive symptom management

In addition to rationalising medications and interventions, it is wise to consider what medications may be required as part of symptom management in end-of-life care. We call this pre-emptive prescribing. This can be incredibly reassuring for family members and other healthcare professionals in reducing anxiety about unmanaged symptoms. Other chapters in this book provide an extensive

and comprehensive review of medications for different symptoms. The list below serves only as a prompt for potential symptoms when a patient is reaching the last few hours to days of their life.

- Pain – typically managed in the first instance with basic analgesics such as Paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) but may need escalation to opioids. As an example, Morphine may be provided in short-acting (or fast release) and long-acting (or slow release). It is usual to establish what dose may be needed by using short-acting opioids first before converting to long-acting versions if appropriate. Opioids can be delivered enterally (e.g. orally, or via nasogastric or gastrostomy), intranasally, buccally, intravenously, subcutaneously, transdermally and rectally. Of note, some research has suggested that diamorphine is preferable to morphine when given via the buccal route. Adjuvants may also be helpful and effective alongside opioids in managing specific types of pain.
- Secretions – including the ‘death-rattle’ can be a particularly distressing symptom for family members. Communication is key here and family should be pre-warned about this. It typically occurs when the CYP reaches a state of reduced consciousness and is no longer able to cough or swallow the secretions in their large airways. This does not usually cause any distress to the patient, but the sound may be a concern for family members. Reassurance should be given, as well as positioning of the CYP’s head to allow secretions to drain. If the CYP is thought to be distressed, gentle suction may be considered and/or the addition of an anticholinergic medication such as hyoscine or glycopyrronium.
- Breathlessness/dyspnoea – may again be perceived as distressing by the family but should only be treated when thought to be disturbing the CYP. There is some evidence that low dose opioids and/or benzodiazepines can be effective in relieving the sensation of breathlessness. However, the most effective uncomplicated treatment is to provide movement of air across the CYP’s face e.g. by way of an open window or use of a fan.
- Agitation – this is sometimes described as terminal agitation and may be manifested in many ways. In the first instance it is important to try and determine if there is an underlying cause e.g. discomfort in positioning, pain or other untreated symptoms (e.g. constipation), inability to communicate. Where possible the likely cause should be treated. CYP may experience transference of their family’s distress, and this should be addressed when recognised. There is value in communicating and trying to reassure the CYP (and their family). Benzodiazepines may also have a role here.
- Seizures – may occur as part of the CYP’s underlying condition, or more rarely as a new symptom. Acutely, these may be treated with benzodiazepines. In some circumstances, a specific personalised plan may need to be considered (e.g. with progression to an infusion).
- Bleeding – in some conditions, there may be risk of a significant bleed or ‘catastrophic haemorrhage’. In this case, dark towels should be recommended and high-dose benzodiazepines may have a role in relieving acute distress to the CYP.
- Feeds/fluids – and specifically artificial nutrition/hydration are covered in the Hydration & Nutrition at the End of Life chapter. As a patient reaches the end of their life, their organs (including kidneys) begin to fail and shut down. As part of this, fluid requirements are reduced and urine output falls. It is therefore normal for fluid requirements to decrease. This process should be explained to the family to reduce anxiety. Thirst is not typically an issue,

though wetting the mouth/lips may provide some comfort (for both the CYP and the family). Reducing fluid intake may also help reduce respiratory secretions.

In some cases, it can be helpful to deliver a continuous dose of some select medications to keep a patient comfortable and avoid the peaks and troughs of bolus medication. This is traditionally given via a syringe driver to provide a continuous subcutaneous infusion (CSCI) but can also be given intravenously. Compatibility of medications that can be mixed in the same syringe should be considered.

## What to do when the CYP dies

The family (and supporting health professionals) should know what to do when the CYP dies. In most cases where death is expected and the process has been agreed in advance (with the lead doctor), there is no urgent need to do anything. In the UK, the CYP must be 'verified' to have died by a trained practitioner (often but not exclusively a doctor). This will involve basic checks of the neurological, respiratory, and circulatory systems to confirm that the CYP has died. There is no need for this to happen immediately, but it is typically done within a few hours of death. There is also a legal requirement for a medical practitioner to complete a 'Medical Certificate of Cause of Death' (MCCD) which allows the death to be formally registered. It is recommended that the MCCD is completed promptly as it must be presented to be registered within five days of the CYP's death. Where relevant, a death may need to be discussed formally with the Coroner and this would delay the completion of the MCCD. In the UK, there is a move towards having all patient deaths discussed with a Medical Examiner prior to issuance of the MCCD. The Medical Examiner is likely to be based at a local hospital, and such conversations may be able to occur pre-emptively.

It is vital that somebody – usually the team caring for the CYP when they die – promptly takes responsibility for informing the wider health professionals and team involved with that CYP. This is professional courtesy, but also reduces risk of the family being contacted by somebody who is unaware of the situation.

Respect should be given to observe the cultural and religious beliefs of the deceased CYP (and their family) in care of their body. There may be an option for the body to be cared for in the family home or at a local hospice with use of special 'cooling' equipment. This is also an opportunity for further memory making and to consider any mementos like taking a lock of hair, or hand/footprints that can be made into art or jewellery. Other families will want to arrange a funeral in a short-time period and where possible this should be known of in advance so that the MCCD can be issued quickly.

The family should be given the details of an identified 'key person' who can be their point of contact to support them through the process and direct them to other avenues of support. Particular consideration should be given to siblings and grandparents who may also need additional support. Some charities (e.g. children's hospices, and other specific purpose organisations) can offer bereavement support and this should be explored.

Finally, the staff involved in caring for the CYP may require looking after. Supervision sessions (sometimes called debriefs) can be held in groups and/or individually to give staff an opportunity to celebrate what went well, and to reflect on things that could be improved upon. These serve as opportunities for reflection and service improvement and may also build resilience and sustainability in the team.

## Summary

The dying phase may be weeks, or just a few hours, but communication and planning remain key in aiming to facilitate a 'good death'. The actions you take and the impact you have at this time may change the way the family cope with that death, and this could impact them for years to come. This is a huge responsibility, but also a great privilege. Being honest and explaining the process along the way may be the best gift you can give.

***“If there’s a chance tomorrow that we’ll be apologising because this person died and nobody warned [the family], that’s a far worse conversation for them to have to have.”***

Dr Kathryn Mannix, 2018

## 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 March 2022. 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<sup>1</sup>.

#### Decision making model

Decision making must be made on the grounds of the **best interests**<sup>2</sup> of the child. The best interest's 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 person with parental responsibility or surrogate decision maker to accept their advice.

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#### References

<sup>1</sup> General Medical Council. Treatment and Care Towards the End of Life, 2010.

<sup>2</sup> 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*

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 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.

### Capacity

A person **with capacity** has the ability to make a particular decision, or take a particular action for themselves at the time the decision or action needs to be taken.

### Tests for capacity

An adult of 18 years or over (16 or over in Scotland) 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<sup>3</sup> an adult with capacity may apply for another adult to have Lasting Power of Attorney to make health and welfare decisions on their behalf, should they subsequently lose capacity. The Court of Protection 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

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<sup>3</sup> Mental Capacity Act 2005 Code of Practice HMSO 2007



(IMCA)<sup>4</sup>. 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.

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<sup>5</sup>.

### **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 child's parents or those with parental responsibility must be kept fully involved.

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.

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<sup>4</sup> Making Decisions: Office of the Public Guardian Independent Mental Capacity Advocate Service OPG606

<sup>5</sup> General Medical Council. Treatment and Care Towards the End of Life, 2010.

## 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.<sup>6</sup>

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

The Nuffield Council on Bioethics<sup>7</sup> 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 in the future on the child?
- What benefits will / might the child get from the treatment in future?
- 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 them<sup>8</sup>.
- 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.

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<sup>6</sup> 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*

<sup>7</sup> Nuffield Council on Bioethics. *Critical care decisions in fetal and neonatal medicine: ethical issues*. 2007

<sup>8</sup> General Medical Council. *Treatment and Care Towards the End of Life*, 2010.

- 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 team. 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 as 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.<sup>9</sup>
- 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 considered 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<sup>10</sup>. 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 an 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 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

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<sup>9</sup> General Medical Council. Treatment and Care Towards the End of Life, 2010.

<sup>10</sup> An NHS Trust v MB [2006] EWHC 507 (Fam)

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.

## Specific situations

### Withholding or withdrawing life prolonging treatment

The RCPCH<sup>11</sup>, describes circumstances when withholding or withdrawing life sustaining treatment may be ethically permissible

There are three categories:

1. When life is limited in quantity because of
  - a. Brainstem death or
  - b. Imminent death or
  - c. Inevitable death
  
2. When life is limited in quality due to
  - a. Burden of treatment or
  - b. Burden of the underlying condition or
  - c. Lack of ability to benefit
  
3. When a young person undertakes informed competent refusal of 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 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.

An individual with Lasting Power of Attorney for Health and Welfare or a Court Appointed Deputies can contribute information regarding an individual's best interests and likely preference but they cannot *make* the decision to withdraw life sustaining treatment<sup>12</sup>.

### Clinically assisted hydration and nutrition

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<sup>11</sup> RCPCH Making decisions to limit treatment in children with life threatening and life limiting conditions 2015

<sup>12</sup> Mental Capacity Act 2005 Code of Practice HMSO 2007

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 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<sup>13</sup>.

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 that clinically assisted nutrition or hydration would always be offered if it is of overall benefit; 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.

There is no longer a requirement for a court ruling 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<sup>14</sup>.

### **Cardiopulmonary resuscitation**

Cardiopulmonary resuscitation is like any other potentially life-prolonging medical treatment and the same principles of decision making in the patient's 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 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

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<sup>13</sup> General Medical Council. Treatment and Care Towards the End of Life, 2010.

<sup>14</sup> *An NHS Trust and others v Y (by his litigation friend the Official Solicitor) and another* 2018

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.

## **Consent and refusal of treatment**

### **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 apprised 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.

### **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.

### **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. For example because they were not fully cognisant of the consequences of refusal of treatment<sup>15</sup>.

### **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. However they cannot make legally binding advance decisions<sup>16</sup>.

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<sup>17</sup> (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<sup>18</sup> and Northern Ireland<sup>19</sup>, although this has not yet been tested in the courts.

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<sup>15</sup> Re M (Medical Treatment: Consent) [1999] 2 FLR 1097

<sup>16</sup> Mental Capacity Act 2005 Code of Practice HMSO 2007

<sup>17</sup> 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

<sup>18</sup> 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.

<sup>19</sup> 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.

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.

### **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.

### **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.

## **Issues with decisions**

### **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.

**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 carries 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.

**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 a regular basis.

**Other issues**

**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.

**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:**

Provide the best service possible within the resources available.

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

## Putting theory into practice

### Using a balance sheet

It can be very difficult, when faced with a complex clinical and ethical dilemma to separate out the underlying ethical questions and identify the relevant aspects of the ethical and legal guidance. A balance sheet is particularly useful way of exploring the ethical and legal issues from all perspectives and identifying a way forward. Several examples of balance sheets are available: one of the most useful is appended in Table 1. The key to using a balance sheet is to start by identifying the available options. Often a multidisciplinary team meeting involving multiple specialties will be needed to fully explore and identify the available options.

In a complex situation there will be several options. Each option needs to be considered separately. For example each of the following could be considered as separate options for the same patient:

- To start total parenteral nutrition (TPN) with a view to long term TPN if successful
- To start TPN as a short-term treatment to ascertain whether the patient's overall condition improves with improved nutrition
- Not to start TPN

Once the options have been clearly delineated a balance sheet needs to be completed for each option. Each balance sheet will include the advantages and disadvantages of the option under consideration. It is important to include the perspectives of the child or young person, where applicable.

The best decision (or the least bad decision) is the one that is made as carefully as possible considering all available options. The balance between the available options may be very close. In

this situation the patient, where they have capacity, or those with decision making responsibilities will have the deciding say.

**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.

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 on-going support<sup>20</sup>.

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.

**Table 1 : Balance sheet**

<b>Medical</b> Outcome, benefits and burdens of treatment	<b>Welfare</b> Impact on the way the person lives their life	<b>Social</b> Impact on relationships	<b>Emotional</b> How will the person feel or react	<b>Ethical</b> Any specific ethical issues that require separate consideration
<b>Advantages/ benefits</b>	<b>Advantages/ benefits</b>	<b>Advantages/ benefits</b>	<b>Advantages/ benefits</b>	<b>Advantages/ benefits</b>
<b>Disadvantages/ dis-benefits</b>	<b>Disadvantages/ dis-benefits</b>	<b>Disadvantages/ dis-benefits</b>	<b>Disadvantages/ dis-benefits</b>	<b>Disadvantages/ dis-benefits</b>

<sup>20</sup> Gillis J. “We want everything done” Archives of Disease in Childhood; 93(3): 191-6 2008

## Hiccup

[84]

Hiccup (also known as singultus) is a common symptom, intermittently experienced by everybody of all ages.

It is caused by an autonomic reflex action causing involuntary contraction of the diaphragm and intercostal muscles, leading to inspiration of air, followed by a sudden closure of the glottis, resulting in the classical “hic” sound.

Hiccups are very common in all age groups but especially children and are usually a mild and self-limiting condition requiring no formal treatment. However, if they are persistent (lasting over 48 hours) or intractable (lasting over one month), they can have a profound adverse impact on quality of life and can cause symptoms such as feeding and sleeping difficulties, and increased pain.

Hiccups in palliative care are often multifactorial in origin, and so it is important to consider the likely contributory factors and target any treatment accordingly.

The most common cause of hiccups is gastric reflux and distension – due to ingestion of fizzy drinks, swallowing air, eating too much or too fast, gastrointestinal reflux, or especially in palliative care where gastric stasis or delayed gastric emptying may be present. Other triggers can include emotional stress, sudden temperature changes, spicy foods, alcohol etc.

### Causes

The causes of hiccup can be broadly divided into peripheral and central causes.

Peripheral causes are usually triggered by irritation of the phrenic or vagus nerves. They can be subdivided into gastrointestinal causes such as reflux, gastroparesis, gastric irritation and non-gastrointestinal causes such as pneumonia and other chest infections, asthma, etc.

Central causes can be subdivided into neurological causes such as brain tumour, brain infections or brain trauma, non-neurological causes such as infection, metabolic such as electrolyte imbalance, iatrogenic (from use of opiates, dexamethasone, chemotherapy agents for example), or from hypocapnia triggered by over breathing due to stress, fear, or anxiety.

Other potential causes should be considered and addressed before pharmacological intervention is considered – correction of metabolic causes where possible, strategies to reduce stress and anxiety, stopping or reducing medication known to potentially exacerbate hiccup such as opioids, dexamethasone, chemotherapy agents and simple strategies to reduce gastric distension such as adjustment of feeds, regular winding, posture to reduce reflux.

## Treatment

There is no need to treat hiccup if the symptoms are mild, self-limiting, short lived and not causing undue distress. Medication should be avoided unless nonpharmacological measures have been tried unsuccessfully. These include breath holding, Valsalva manoeuvre, and other measures to stimulate nasopharyngeal irritation such as sipping iced water, eating granulated sugar off a teaspoon, and rubbing the soft palate with the tip of a swab, or pulling on the tongue. If diaphragmatic irritation is thought to be a causal factor this can sometimes be alleviated by leaning forwards and pulling the knees up to the chest. Similarly, if hypocapnia due to stress and anxiety has triggered hiccups this can sometimes be helped by rebreathing into a paper bag.

If drug treatment for hiccup is deemed to be necessary, therapy should be targeted depending on the underlying cause if known, started at the lowest dose, titrated according to response and ideally discontinued once the hiccups have been brought under control.

For PERIPHERAL causes, simple over the counter remedies such as peppermint water or an antifoaming agent such as simethicone may offer simple effective relief, especially with upper gastrointestinal causes. If more formal prescribed medication is required, first line treatment should be a PPI as the most common cause is gastric irritation and reflux. Metoclopramide is an alternative, but only in a palliative care setting as neurological side effects limit its use especially in a paediatric population. Second line options include Baclofen or Gabapentin, with Chlorpromazine or Midazolam being third line agents.

For CENTRAL causes, Baclofen, for its GABA receptor agonist activity, is usually recommended as the first line agent of choice in adults, although there is little evidence for this in children. It is used widely for other indications in children. Second line drug of choice is Gabapentin, and third line suggestions include Haloperidol and Calcium channel blockers such as Nifedipine, which may block the hiccup reflex arc.

For troublesome hiccup in the terminal stages of life, Midazolam is often used for other end stage symptoms and may help to suppress the hiccup reflex so is a useful agent in this situation.

If the combination of non-pharmacological and pharmacological measures has proved ineffective, interventional techniques such as vagal or phrenic nerve blocks have been used, but this would need very careful assessment of risk/benefit profiles in a palliative care setting. Acupuncture may be worth trying although there is no direct evidence base to support its use for this indication.

## Gastro-oesophageal reflux

[12, 85-96]

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, which 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 its use is 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

[97-110]

## 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 into 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.

## Hydration & Nutrition at the End of Life

[73, 111]

Appropriate hydration and nutrition are seen as a basic element of care. At a social and cultural level, to be hungry or thirsty is a discomfort that anyone can relate to, and a harm that we seek to protect people from wherever possible. Feeding and being fed is usually seen as a source of pleasure and a sign of love, and for some children for whom artificial feeding has always been necessary it will have been an important element of the caring relationship. When a child or young person is no longer able to eat or drink (either unaided or with the help of others), it is often unclear whether the possible benefits of medically assisted hydration or nutrition at the end of life outweigh the harms.

When making decisions about this, healthcare professionals need to be mindful of the strong social, cultural, and moral imperative to avoid any sense of a child or young person suffering because of lack of fluids or food. When considering the benefits and harms of artificial hydration or nutrition, it is also essential to consider if and when it ceases to be in the child's best interest, or when it may even be harmful to a child or young person reaching the end of their life.

While it is important to ensure that, where appropriate, hydration and nutrition are provided in the most effective manner, there may be situations in which this is clinically inappropriate. Given that the withholding or withdrawal of hydration or nutrition may play against very basic human instincts, the issue needs to be handled sensitively and the feelings of the parents, family and carers must be acknowledged. Where there are clinical signs that suggest that continued artificial hydration or nutrition may no longer be in the child or young person's best interests, it is imperative to establish the best means of keeping them comfortable, to reassure the parents or carers and family, and to help them understand the continued value of providing appropriate mouth care and other comfort measures. Careful communication will help to ensure that families are not burdened by understandable but avoidable concerns around this issue. Taking less food and drink at the end of life may even be, to a degree, a physiological adjustment. 'Forcing normal hydration' onto a person at this time may indeed add to their burden.

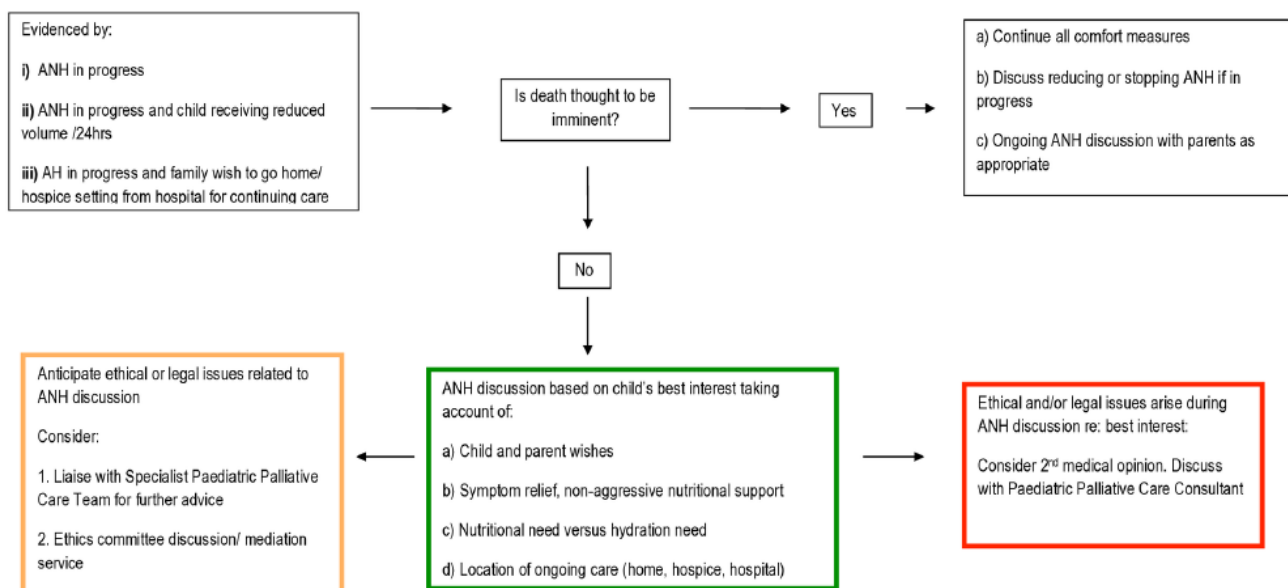
It is important to take account of guidance and general principles on this issue published by health professional bodies such as Royal College of Paediatrics and Child Health (RCPCH), (Larcher, 2015) and the General Medical Council (General Medical Practice, 2010). These recognise that decisions must be made within a legal framework and that where there is significant and unresolvable disagreement between families and healthcare professionals around withholding or withdrawing medically assisted hydration or nutrition, specialist mediation and/or legal advice should be sought.

**NICE (NG61) made the following recommendation regarding hydration & nutrition at the end of life:**

- If a child or young person with a life-limiting condition is approaching the end of life or is dying, discuss how to manage their fluid needs with them and their parents or carers.
- If a child or young person is dying, encourage and support them to drink if they want to and are able.

- If a child or young person is dying, continue to provide them with lip and mouth care.
- If a child or young person is dying and cannot drink, discuss with them (as appropriate) and their parents or carers whether starting or continuing enteral tube or subcutaneous or intravenous fluids is in their best interests.
- Be aware that enteral tube and subcutaneous / intravenous fluids may have a significant effect on care, may be a burden for children and young people, and may mean the place of care and place of death need to be changed.
- If a child or young person is given enteral, subcutaneous, or intravenous fluids, review this decision regularly to make sure it continues to be in their best interests.
- If a child or young person is approaching the end of life or is dying, discuss how to manage their nutritional needs with them and their parents or carers.
- If a child or young person with a life-limiting condition is dying, encourage and support them to eat if they want to and are able.
- If a child or young person is dying and they are receiving enteral tube feeding or intravenous nutrition, discuss with them (as appropriate) and their parents or carers whether continuing this is in their best interest and review this decision regularly.

The key components of decision making are summarised below:

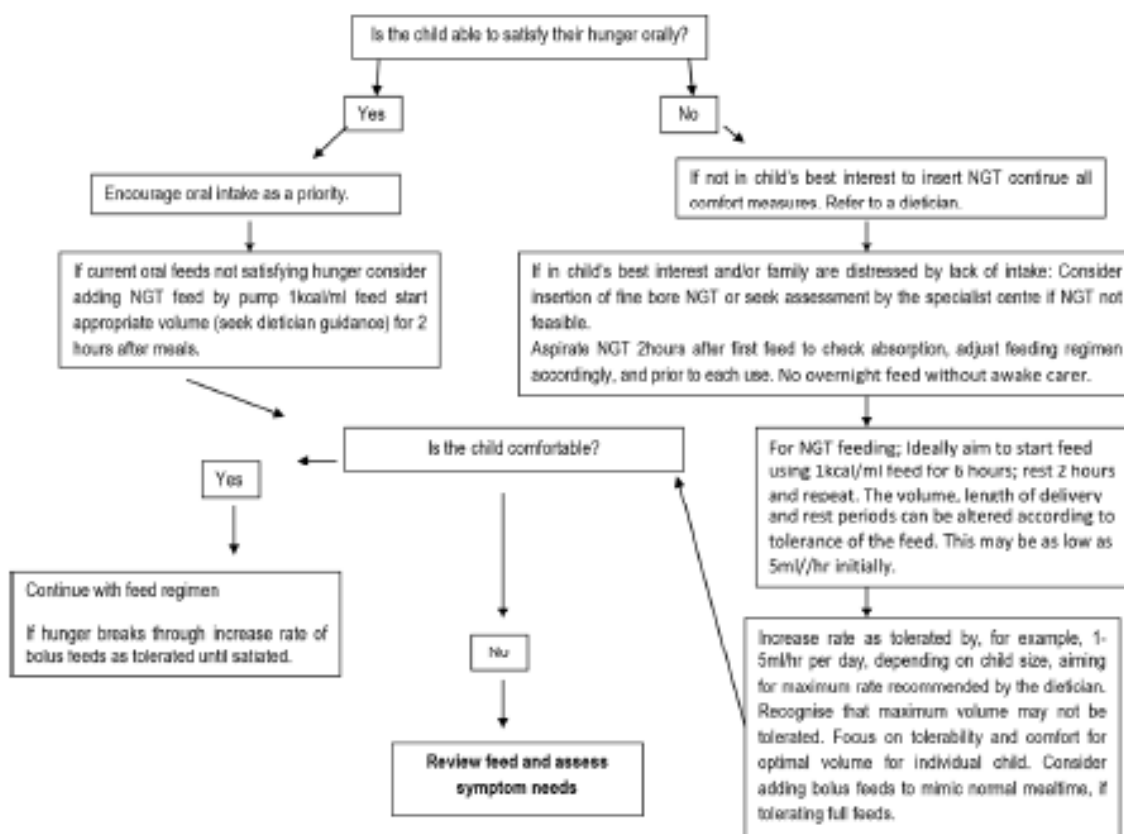


**Professional decision-making algorithm for artificial nutrition and hydration (ANH) management**

From and with permission: *Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres Anderson A-K, et al. BMJ Supportive & Palliative Care, 2019.*

## Enteral Feeding in the Context of End-of-Life Care

The aim is likely to be the provision of the most enjoyment or comfort from enteral intake, with the least burden and some tolerance of carefully managed risks related to aspiration. Quality of life will be a more important consideration than nutritionally complete intake.



Enteral feeding plan at end-of-life care in community setting for over 1 year of age. NGT, nasogastric tube.

From and with permission: *Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres Anderson A-K, et al. BMJ Supportive & Palliative Care, 2019.*

## Comfort or 'taster' feeds

These feeds are comfort-oriented in that they are the least invasive and potentially the most satisfying way of attempting to maintain nutrition. In children towards the end of life, comfort feeds can be administered through an individualised oral feeding plan, where the main goals are enjoyment of small amounts of food or drink, and where hunger may often be ameliorated but may

not provide optimal nutritional benefit. Despite there being a level of risk for aspiration, children and professionals may tolerate a higher risk burden to allow the child some feed enjoyment in line with their disease progression. The intervention may be as small as a taste to the lips of a preference food, but can include ice chips, jelly, fragments of chocolate in the buccal pouch etc.

## Blended diet and Nutrition

[112-126]

### What is a blended diet?

Children and young people with life limiting illnesses, particularly some with neurodisability and an unsafe swallow, may be fed via gastrostomy.

In many countries, the default is to use liquid, nutritionally complete, pre-prepared commercial feeds which are standardised and easy to administer via the gastrostomy. However, families are increasingly keen to use blended (liquidised, puréed) 'table food' instead of, or in addition to, prescribed feeds. This is a reasonable option for children over 1 year old.

Research is under way to clarify the benefits and risks of this approach: to date there are anecdotal reports of benefit and little evidence of harm.

Pending clearer research evidence, the British Dietetic Association have produced an excellent 'Practice Toolkit', available here <https://www.bda.uk.com/uploads/assets/33331d33-21d4-47a5-bbb79142980766a7/FINAL-Practice-Toolkit-The-Use-of-Blended-Diet-with-Enteral-Feeding-Tubes-NOV-2021.pdf>. This also includes evidence tables, an example risk assessment, and monitoring proforma. Dieticians are now supported by the BDA in offering a blended diet as an option 'where they believe there to be potential physiological, social or emotional benefits to the tube-fed individual and their family' <https://www.bda.uk.com/resource/launch-of-bda-practice-toolkit-the-use-of-blended-diet-with-enteral-feeding-tubes.html>.

### What are possible benefits of a 'blended diet'?

From questionnaire surveys and individual interviews with parents, families have told us about these benefits when using a blended 'table food' diet:

- Improvements in gastro-oesophageal reflux, vomiting and constipation.
- Improvements in skin and hair.
- Some children can come off some of their medication, particularly for gastro-oesophageal reflux and constipation.
- Improved wellbeing; improved longer term health.
- May be better tolerated than pre-prepared feed.
- Improved appetite and nutrition.
- Some children gain significant weight.
- Meals can be individualised (and varied).
- Psycho-social benefits, with children being more integrated into normal family life, included in family mealtimes and celebrations, able to order meals in restaurants etc.
- Families may be more likely to accept a gastrostomy if they know tube-feeding does not automatically exclude the option to still cook for their child.



## What are possible risks of using a blended diet and how can they be managed?

- For those who stop using a blended diet, there is little data yet as to whether this is mainly due to practical considerations (preparation can be time-consuming), possible adverse effects, and/or lack of clear benefit.
- The BDA Toolkit has a helpful risk assessment template and troubleshooting guidance.
- Hospice-specific guidance documents help in relation to hospice-specific risk management.

a) *Tube blockage and damage*: See advice here:

<https://www.nursingtimes.net/clinical-archive/gastroenterology/peg-tubesdealing-with-complications/5076347.article>

b) *Infection* (the food is non sterile): follow national food hygiene guidance, using the same hand and equipment hygiene practice as for prescribed enteral formula.

c) *Unknown and variable nutritional content*: provide dietetic support on portion sizes: use dietary analysis to meet estimated nutritional requirements.

d) *Potential micronutrient deficiency*: clinical impact of unpredictable and possibly deficient micronutrient content is unknown. Dietetic analysis and support are helpful. Many suitable liquid vitamin preparations can be given via gastrostomy. Mixing prescribed feed and liquidised food should reduce variability.

e) *Altered medication absorption (toxicity or under-dosing may occur due to altered absorption)*: this requires continued vigilance, especially when liquidised food via gastrostomy is commenced or the proportion of liquidised food changes, and during acute illness.

f) *Syringe connection issues*: note guidance has changed in relation to syringe ends since the transition to ENFit-compatible equipment. ENFit enteral feed equipment has become the UK standard. ENFit-compatible equipment may have an impact on the ease of delivery of liquidised food. Bladder/ catheter tip syringes are no longer available for enteral use.

g) *Economic and secondary impacts*: note some community nutrition nurse support is provided by feed companies, as part of local contract agreements. This service and the delivery of ancillary equipment is funded from prescriptions for prescribed formula. Reducing use of prescribed commercial feeds could save the NHS money but would be more costly for local services which may have to fund more support and delivery services.

Additional costs to families of liquidised food would include food purchase, provision of equipment including a blender, and the significant additional time and organisation required for learning about nutritional content of foods, planning, hygienic preparation and storage of liquidised food.

## Who can have a Blended Diet?

Many families have carried out research via the internet /social media and have made up their own minds about starting a blended diet independently. However, ideally a local Trust decision pathway, involving parents, carers, patient and health professionals would initially address this if interest is shown in feeding by this method.

### Considerations

#### Type of gastrostomy device

A low-profile device is recommended. The feeding tube should ideally be at least 12Fr diameter. Narrower tubes are sometimes used, but the blend may need to be thinner in consistency. If the device is a PEG, then a further risk assessment must be done to risk manage the event of blockage, including planning for how to maintain nutrition and fluid intake until the tube can be changed or unblocked. ***Input by surgical team, more detailed guidance by dietitian needed -some Trusts may not support feeding blended diet via a PEG.***

Feeding blended diet by naso-gastric tube or a jejunostomy is not recommended and is likely to be less safe than gastrostomy feeding.

#### Is a blended diet appropriate for this child or young person?

If the feeding device is a low profile one, then this is appropriate but there may be situations that the professional team need to consider e.g., any difficult medical, safeguarding or other contraindications.

## How to start a blended diet

### Equipment Required

- **Blender:** A high powered blender such as Vitamix, Blendtec, Optimum and Omni-blend allows blending to a smooth paste. These are all expensive industrial blenders, but they may be a better long-term investment. Other companies such as Nutri-bullet and Nutri Ninja have recently produced very good economical blenders. A hand blender and a fine metal sieve may work with soft easy to blend foods or when trialling a blended diet before investing in more expensive equipment.
- **Syringes:** 60ml syringes that have a single/thin O ring (rubber washer inside the syringe).
- **Extension sets:** A right angled extension set helps to prevent blockage by catching stray lumps and is easier to plunge through.
- **Freezer safe plastic food containers, bottles or pouches** are all useful to store food in.
- **Syringe caps,** allow pre-filling syringes with blends and water.

- **Cooled freshly boiled water** or freshly drawn tap water for flushing.
- **Blended Food.**
- **Paper tissues.**

**Tube care** should follow specific manufacturers' guidelines (care of gastrostomy button and washing and drying of extension tubes and syringes).

## Practical tips for introducing blended diet

### 1. Some options for starting to use a blended diet via gastrostomy:

- *Start with blended diet top-ups*, one meal at a time. Give a small amount of blended diet at the usual feeding time and top up the volume with commercial feed. Build up the blended amount and gradually reduce the commercial feed with time over a few days.
- *Start with snacks*, as these are between feeds and don't impact on the current feed regime. Introduce a commercial stage 1 purée weaning meal at a quieter time of day. This can help to test the practicality of giving blended food and assess tolerance. Then switch to a blended family meal matching the volume of the child's commercial feed, one meal at a time.
- *Substitute the equivalent volume of a commercial feed with a blended family meal each day*, and gradually increase the feeds substituted each day, as tolerated. Plating up the meal first can help gauge appropriate portion size. Then blend the meal to the correct consistency, using water or more nutritious fluids, and slowly administer.
- *If a child or young person eats orally but requires topping up via their gastrostomy*, plate up the amount they would have, offer orally and then blend the remainder to give via gastrostomy.

### 2. Practical options once established on blended diet include:

- Blending meal by meal by meal.
- Blending the full day's meals together and then dividing it up for the day.
- Blending a savoury meal with the dessert. This does not affect the nutrients in the blend.
- A proportion of the commercial feed can be retained as part of the meals to help meet nutrient requirements or to make the diet more feasible practically.

**If there is concern about volume tolerance**, slow down the rate of plunging the food, perhaps taking small breaks during the feed, then gradually increase it again.

**If there is concern about nutritional adequacy**, after monitoring growth, extra calories can be provided by:

- Increasing the portion sizes.

- Increasing protein and calories (use the Eatwell guide to identify protein and fat containing foods).
- Check for over-dilution of blended food with too much water. More nutritious fluids such as commercial tube feeds, infant formula, full fat cow's milk, any plant-based milk (e.g., coconut, oat milk) could be used instead).
- Energy dense, nutrient-rich calorie boosters can easily be added to blended meals e.g., avocado, full fat dairy products such as cheese or full fat yogurts, nut butters, ground nuts, hummus and fruit juices.
- Fats, oils, cream, and sugary foods such as honey and syrup are useful, but do not contribute other valuable nutrients.

## Fluid

It is important to consider the overall fluid provision from a blended diet, including accompanying water flushes. They should both match the volume that would have been prescribed on feeding with a commercial feed and flushes.

The fluid content of a blended diet is likely to be lower than a commercial feed (approximately 50% of blended food volume is likely to be fluid).

A dietitian can give guidance of fluid requirements for a child /young person's age and weight.

Water can be added to feeds to provide extra fluid. But it may be advisable to use nutritious fluids such as milk, gravy, or fruit juices to avoid diluting the nutritional content of the blended meal, particularly if poor weight gain.

**Feeding Method - How to administer blended diet in practice:**

There is a useful introductory video about using blended diet here:

<https://www.youtube.com/watch?v=WEaKkl2zzMM>.

A full series of other relevant videos relevant to gastrostomy feeding is here:

<https://www.oxstar.ox.ac.uk/more/supporting-parents/watch-the-videos>

Some parents and carers give water at least 45 minutes before blended food as this may speed up gastric emptying, helping to clear any previous feed and gastric juices, preparing the stomach to receive food, as well as providing additional fluid.

Prime the extension set with cooled freshly boiled water or freshly drawn tap water. Re-fit the extension set and draw up 60mls of blended food. Ensure no air has been accidentally drawn up into the syringe.

Administer into the gastrostomy at roughly 1ml per second by gentle push on syringe plunger. Tip: Use the ml markers on the syringe barrel – one second per ml (the rate may vary depending on individual tolerance).

Rest for a few seconds between syringes.

Aim for the blended food to take approximately as long as the child or young person would take to eat the meal i.e. a full plate of food should take roughly 20-30 minutes.

Supporting the parent /carer's feeding arm will avoid potential tugging on the gastrostomy tubing if starting to tire.

**Flushing** - Flush thoroughly with a good volume of water at the end of administering blended food.

It may be helpful to flush with 5-10ml of water between individual syringes of blended food, particularly for a thick blend.

Children on a blended diet often tolerate larger water flushes after feeds, aiming for 30-60ml water flushes.

## Guidelines for preparation

### Consistency

- Blended diet meals should be a smooth, thin puree or double cream consistency.
- The correct consistency will have no “bits” or lumps in it and run easily off a spoon.

### Blended Meal Planning / Portion sizes

- All children and young people are different, particularly those with additional or complex needs. They each have their own individual energy requirements.
- It is important to start with an age-appropriate level of food as a guide and, then adjust up or down depending on tolerance and growth/ weight gain. *See resources section.*
- There are some resources available to help with portion sizes and balance of macro nutrients (i.e. carbohydrate, protein, and fat).
- Agree a plan to monitor an individual’s growth with a dietitian or the healthcare team.

## What to do if the child is ill

In acute illness, it can be difficult to monitor and maintain adequate hydration and children are at greater risk from contaminated food. Short term adjustments to the regime may be needed, and some families revert to giving pre-prepared feeds during acute illness, especially during hospital admissions.

### Sickness and diarrhoea:

- Omit the blended diet. Continue to give plenty of fluid (water or Dioralyte) in its place to keep well hydrated (can be administered by pump or gravity bolus).
- Once vomiting/loose stools have subsided, re-introduce blended food gradually using smaller volumes, and foods that are plain and easy to digest. (Omit high fat /calorie boosters at this stage) Take care with large amounts of fruit/veg/smoothies. Extra fluid may still be required.

### Coughs and Colds

- Continue usual blended diet but may need to decrease amounts if a child is struggling with the volume (excess mucous may sit in the stomach, affecting volume tolerance and digestion).
- Extra fluid flushes are needed if volumes of blended food are decreased.

### Admission to Hospital:

Check hospital regarding local policy around feeding a child on a blended diet.

## Food Safety and hygiene

The same principles of preparing food for oral consumption apply to the preparation of blended diet for enteral feeds: <https://www.food.gov.uk/food-safety>

- Parents/carers /staff can complete on-line food hygiene training, based on national food safety guidelines.

- Good hand washing techniques must be adopted, and hands washed prior to handling food or equipment.
- Cooking and liquidising equipment should be of a design which can be thoroughly cleaned, manufacturers' instructions on cleaning blenders should be followed.
- Surfaces on which food is prepared must be clean.
- Food must be stored correctly prior to cooking or use.
- Food must be cooked thoroughly prior to liquidising and prepared as closely as possible to the time of administration.

### **Storage, batch cooking, freezing, defrosting, reheating**

If it is necessary to store food in the fridge for later administration, the following guidelines should be adopted:

- Store the food in a clean container with a lid or covered dish on the top shelf of the fridge.
- Cool food as rapidly as possible and store in the fridge as soon as is cool enough.
- Blended food should not remain at room temperature for more than 2 hours and should be discarded after this time if not used.
- Blended food that will not be used immediately may be refrigerated (below 5 degrees C) for up to 24 hours after preparation.
- It is preferable to have a fridge thermometer to monitor the temperature of the fridge.
- Blended food may be frozen (below -18 degrees C) for up to 1 month.

### **Reheating**

Administering the food at the desired temperature can be achieved in the following ways if it is not administered immediately after cooking:

- **For pre-cooked, mixed meals:**  
Remove food from fridge, transfer to a suitable container, and microwave until 'steaming hot' or 'piping hot' throughout (or if using a thermometer, a minimum of 70° C for at least 2 minutes). Stir well before serving. Allow to cool to body temperature (37° C) or below before giving.
- **For foods that would normally be eaten cold e.g., desserts, fruit blends or prepacked baby foods:**  
Remove feed from fridge and stand on work surface for 30 minutes to allow this to come to room temperature (WHO, 2007). Or remove feed from fridge and place the container in a jug of hot water for no more than 10 minutes. Shake or stir before feeding.

### **Defrosting**



- Frozen blends should be either defrosted in the fridge overnight or using the defrost setting in a microwave.
- Food should be reheated in accordance with the information above. 'Reheating' section.
- Use defrosted feeds within 24 hours of removing from the freezer.

## Resources:

### 1. **Blended diet:**

- **BDA Blended Diet Practice toolkit** <https://www.bda.uk.com/uploads/assets/33331d33-21d4-47a5-bbb79142980766a7/FINAL-Practice-Toolkit-The-Use-of-Blended-Diet-with-Enteral-Feeding-Tubes-NOV-2021.pdf>
- **BDA Blended Diet Practice** overall resource and associated blog / commentary <https://www.bda.uk.com/resource/launch-of-bda-practice-toolkit-the-use-of-blended-diet-with-enteral-feeding-tubes.html>
- Aadhaar O’Gorman, E (2012). Complete Tubefeeding: Everything you need to know about tubefeeding, tube nutrition, and blended diets.
- Lapwood S, Brown S, Griffith R, Kennedy A, Lewis J (2017). Use of blended / liquidised ‘table food’ diets via gastrostomy: Questions and Answers <https://www.togetherforshortlives.org.uk/resource/use-of-liquidised-table-food-diets-via-gastrostomy-qa/>
- PENG Risk Assessment Template for Enteral Tube Administration of Liquidised Diet <http://www.peng.org.uk/pdfs/hcp-resources/risk-assessment-template.pdf>
- Note this helpful YouTube demo and instructions to ‘make a demo box’ <https://www.youtube.com/watch?v=fFA-AkZ4EEc>
- <https://renacahill.wixsite.com/blended-diet-online/blended-diet-tube-fed-children-uk>

### 2. **Nutrition:**

- NHS Living Well: <http://www.nhs.uk/livewell/Pages/Livewellhub.aspx> . Specific links below:
- <http://www.nhs.uk/Conditions/pregnancy-and-baby/Pages/vitamins-for-children.aspx>
- <https://food.gov.uk/food-safety>
- <https://nutritiondata.self.com/> (US perspective)
- First steps nutrition advice for under 5 year olds: <https://www.firststepsnutrition.org/eating-well-early-years/> 
- Eating Well: First Year of Life, 1-4year olds, 5-11 year olds and 12- 18 year olds <https://www.cwt.org.uk/publications/>
- <https://www.nhs.uk/live-well/eat-well/the-eatwell-guide/>
- What’s Enough - A guide to Age Appropriate Food Portion Sizes:  [www.ndr-uk.org](http://www.ndr-uk.org) :
- NB Nutrition apps are available but not validated e.g. ‘My Fitness Pal’

### 3. **Gastrostomy:**

- See generic information from the NNNG (National Nutrition Nurses Group) re gastrostomy care: <http://www.nnng.org.uk/download-guidelines/>
- Guidance around tube blockage and complications: <https://www.nursingtimes.net/clinical-archive/gastroenterology/peg-tubesdealing-with-complications/5076347.article>
- Also see manufacturers’ websites, for example:
  - o [www.gbukentral.com](http://www.gbukentral.com) (Mini buttons)
  - o [www.vygon.co.uk](http://www.vygon.co.uk) (Mic-key buttons)
  - o [www.appliedmedical.net](http://www.appliedmedical.net) (Bard button)
  - o [www.fresenius-kabi.co.uk](http://www.fresenius-kabi.co.uk) (Freka button)



## HIV and AIDS

[127-137]

### Introduction

Human Immunodeficiency Virus (HIV) disease generates the greatest need for palliative care globally amongst children, with >29% of the children globally needing palliative care, having HIV disease. The impact of this brings great physical, psychological, social and spiritual burden on the children and their families and caregivers. HIV is also a disease that will affect multiple members of the same family, thus the impact of the disease on family members heightens the burden on the children, with many being orphans, and having seen family members die with the disease. The majority of children with HIV who would benefit from palliative care will not be at the end of their life, but are living with HIV, are taking antiretrovirals (ARVs) and coping with the impact on a daily basis. Palliative care has an essential role to play in relieving this burden.

HIV/ Acquired Immune Deficiency Syndrome (AIDS) does not just affect a child's immune system, but it is a multi-system, multi-organ disease. Thus, the impact of the disease physically and psychologically is cross-cutting. However, many of the symptoms that children will experience can be managed successfully, using the same principles that can be applied to other conditions, and therefore utilising the advice on symptom control throughout this handbook. Important also to remember are the four rules of symptom control in children's palliative care:

- a) Don't panic
- b) Immaculate assessment
- c) Hope for the best, and
- d) Treat what you can treat.

Within the care of a child with HIV/AIDS, it is important to treat what you can treat. Many opportunistic infections can be treated, and many can be helped through ARVs – thus both the provision of ARVs and the treatment of opportunistic infections are important. Palliative care remains an essential part of HIV/AIDS care as treatment sometimes fails, is not available or affordable, or the treatment itself may produce side effects and symptoms. You don't need to be an HIV/AIDS expert to provide good children's palliative care, but you do need to know about ARVs, their side effects and possible interactions, along with how to treat opportunistic infections.

## Facts and Figures

In 2020 UNAIDS estimated that 150,000 children (<15 years) were newly infected with HIV, bringing the total number of children globally living with HIV to 1.7 million. 99,000 children < 15 years also died from AIDS in 2020. Unfortunately, in 2020, the number of children receiving ARVs reduced, such that 800,000 children (<15 years) living with HIV were not on lifesaving ARVs and 63% of those were aged 5-14 years of age. Of the daily new infections for both adults and children, 60% were in sub-Saharan Africa, 10% in children < 15 years and 31% amongst young men aged from 15-24, and 20% amongst young women aged from 15-24.

Two thirds of all children with HIV live in Sub-Saharan Africa with an estimated 2.5 million children and adolescents living with HIV in 2020, and 104,000 deaths. Most infections in children in sub-Saharan Africa are through mother-to-child transmission <sup>(5)</sup>, and whilst infections through this route have decreased, they have not yet reached the global target set of reducing mother-to-child transmission to <15,000 children. Infections through mother-to-child transmission (MTCT) are due to a range of reasons including the high HIV infection rate in pregnant women and the coverage and uptake of (Prevention of Mother to Child Transmission) PMTCT programmes. UNAIDS also estimate that 43% of children living with HIV in sub-Saharan Africa have an unknown HIV status and only 38% are on ART and virally suppressed <sup>(4)</sup>.

However, the impact goes far beyond those children and adolescents living with HIV. UNICEF estimate that 11.5 million children aged 0-17 years lost one or both parents to AIDS in 2020. When this happens, children are the first to suffer. Many families will be pushed further into poverty as they care for sick and dying family members, therefore the physical, social and psychological impact is great. Where both parents have died there may be child-headed households as families struggle to stay together and care for each other. Children living with HIV may not have the transport funds to access treatment, or a responsible caregiver to support their treatment regimens and ensure adherence. School fees may no longer be available, or well children may be pulled out of school to farm or earn money for the family, thus education levels decrease and the family spiral deeper and deeper into poverty, often selling cows and belongings to pay for treatment. Alongside this, the stigma associated with HIV continues in many places, thus making it harder for children to get the help and support that they need, many of whom are at risk of discrimination, and physical and sexual abuse.

There continue to be improvements in HIV care and treatment in many low- and middle-income countries (LMICs) however whilst survival amongst HIV-infected children in high income countries (HIC) is good, this is not always the case in LMICs. Many children living with HIV in LMICs have limited access to treatment, basic HIV care or palliative care. However, all children have the right to care and children with HIV should not have to experience unnecessary pain and suffering.

## HIV and its pathology

HIV is a virus which causes the immune system to become weak. It attacks the CD4 cells which are part of the body's immune system. CD4 cells are T-Lymphocytes, which are vital in fighting infection and providing immunity within the body. When a child is infected with HIV, the HIV takes over the CD4 cells and uses them to make more HIV, killing the CD4 cells in the process. Without treatment the HIV takes over more and more CD4 cells and as the child's immune system becomes weaker, their body can no longer fight infection. Sometimes this happens slowly, and the child may be asymptomatic for many years, at other times it can happen quickly. As the number of CD4 cells in the body decreases the child becomes susceptible to various specific types of infection, known as opportunistic infections. When a child's CD4 cells are mostly destroyed they become unable to fight disease and develop AIDS.

The rate of immunosuppression is often faster in children than in adults, with babies born with HIV often becoming sick and/or dying within their first year and without treatment many babies die before they reach the age of two years. This may be because a baby does not have a fully developed immune system and due to the HIV, their immune system does not get the chance to develop fully, so without treatment, they cannot fight the opportunistic infections and will die. HIV infection can also impact the nervous system and this can affect how children grow – impacting on the normal development of movement, speech and understanding.

In untreated children a more rapid progress to AIDS has been seen in 2/3<sup>rd</sup>s of children, with a more slowly progressive disease being seen in 1/3<sup>rd</sup> of children which manifests later in children infected with lower viral loads. However, with ARVs, HIV has transformed for many, from a progressively fatal disease to a manageable chronic condition. This however relies on adherence to treatment and maintenance of viral suppression, possible in HICs but not in many LMICs where access to treatment is limited. Without treatment most children born with HIV will die before their second birthday from complications related to opportunistic infections. Thus it is important to treat opportunistic infections where possible and relieve symptoms to improve quality of life and enable children to return to school or other normal activities. Most can be treated with relatively inexpensive medications, although some need treatments that are more expensive such as for the treatment of cryptococcal meningitis.

The HIV virus can affect the body in two ways: through suppressing the immune system, but also by directly infecting and damaging organs and systems. Organs and systems that can be directly impacted include:

- *The Central Nervous System* – damage to both the central and peripheral nervous systems can cause HIV encephalopathy and both central and peripheral neuropathies. These can cause a range of developmental and cognitive delays, including severe disability and death. Damage to the nervous system can cause severe pain in the arms, hands, legs and feet.
- *The Gastrointestinal System* – damage can cause diarrhoea, mal-absorption and weight loss – with no other explanation than the HIV itself.

- *The heart and kidney* - damage can cause cardiopathy or nephropathy.
- *The respiratory system* – damage can cause lymphocytic interstitial pneumonitis (LIP) and debilitating chronic lung disease.

## Psychosocial issues in HIV/AIDS

Children living with or orphaned by HIV will experience many psychosocial issues – some will be similar to those experienced by any child with a life-limiting illness, yet others will be unique to children with HIV. Such issues include chronic physical health, orphanhood, frequent bereavements (parents, siblings, friends), stigma, physical and sexual abuse. Alongside this, the spiral into poverty impacts on their living conditions, a lack of access to education. These, alongside the effects of the disease itself can induce psychiatric disorders in the infected child, including depression, anxiety and suicidal thoughts.

Good communication is essential within palliative care. Whilst not the focus of this manual, good communication can help in terms of symptom control, as well as psychological care and support. One of the key issues within HIV care with children is when to tell the child about their illness and prognosis. Being open and honest with a child and their family can help reduce anxiety, reduce symptoms and help with adherence to treatment.

## Symptoms in HIV/AIDS

When looking at symptoms in children with HIV/AIDS it is important to think about psychological/social factors and not just focus on the physical. Many children with HIV in LMICs will be orphans, some having seen family members die from AIDS, and many will still experience the effects of stigma. This along with a range of other issues will all impact on the presentation of physical symptoms and demonstrate the importance of the holistic approach. However, we know that less attention is paid to the psychological, social, ethical and cultural aspects of care, with regular screening needed for psycho-social and spiritual distress including psychiatric symptoms such as depression.

A study in Malawi identified the frequency of symptoms experienced by children with HIV/AIDS with weight loss, cough and fever being the most frequent symptoms (See Table1).

**Table 1: Frequency of symptoms experienced by children with HIV/AIDS**

Weight loss	91.8%
Cough	60.3%
Fever	58.9%
Sores in mouth	57.5%
Poor appetite	54.8%
Diarrhoea	47.9%
Pain	30.0%
Vomiting	28.8%
Eye discharge	24.7%
Skin rash	13.7%
Difficulty breathing	9.6%

Advice about how to manage the majority of the symptoms experienced by children with HIV/AIDS can be found in the relevant chapters of this handbook such as fatigue, weight loss, anorexia, nausea and vomiting, sore mouth, constipation, breathlessness, persistent cough, skin care and pressure sores, delirium, agitation and depression. The following table (Table 2), includes some symptoms which may not be covered in other chapters and demonstrates the overlap between treating the HIV, treating opportunistic infections and providing palliative care.

**Table 2: Symptom not covered elsewhere**

Symptom	Causes	Disease specific therapy	Palliative therapy
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.
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.

Ano-genital ulceration	Commonly due to herpes simplex virus. Candidiasis.	Herpes: Acyclovir (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.
Severe dermatitis	Seborrhoea dermatitis Infestations Folliculitis Fungal infection Hypersensitivity Renal and liver disease	Antibacterials/ antifungal/ antiparasitics  Hydration  Steroids	Emollients Antihistamines Antiseptics 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	Acyclovir 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). 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 Acyclovir Chemotherapy	NSAIDS Steroids Hyoscine Cimetidine

Pain remains a problem in children with HIV/ AIDS and is sadly often undertreated. This may be due to children's reluctance to talk about their pain, and health professionals' under-recognition of pain and a lack of knowledge on how to manage it. The use of ARVs helps in preventing pain, but for those without ARVs pain can be a significant issue when opportunistic infections and the HIV infection throughout the body causes headaches, muscle aches, joint pain and tingling or burning in the arms or legs – pains that it can be hard for a child to describe or understand. Physical pain is exacerbated through feelings such as grief, worry, fear and loneliness along with the emotional pain of unkindness and cruelty due to stigma. Pain should be treated as soon as possible and for a child with HIV one of the most important ways to reduce pain for the long term is to give them ARVs. ARVs prevent many illnesses that cause pain. Pain in children with HIV/AIDS may be caused in a variety of ways including:

- The effects of HIV itself.
- The effects of opportunistic infections.
- The effects of medications used to treat HIV e.g., ARVs.
- The effects of a chronic debilitating illness.
- Procedural pain due to repeated procedures.

The list of HIV-related conditions in children that cause pain is long, and it is best to assume that any of the above can cause pain and treat that pain. The principles of managing pain in children with HIV/AIDS are the same as for other children needing palliative care and are covered in the relevant chapter on pain. However, it is important to remember that whilst ARVs can help reduce pain, they can also increase the prevalence of pain, with the prevalence of peripheral neuropathy increasing the longer someone is on ARVs.

## ARVs in CPC

Sadly, since the introduction of ARVs, provision of and access to ARVs for children has always lagged behind that for adults. Despite advances, inequities continue with just 54% global paediatric coverage in 2020 (>20% behind that of adults). Also, the health outcomes of children receiving ARVs are worse than adults, partly due to a lack of paediatric HIV medicines and challenges in retaining children in care. Alongside this, attempts to prevent infection through mother-to-child transmission have continued, with one of the key advances to preventing transmission being the use of lifelong ART for all pregnant and breastfeeding women living with HIV.

Whilst ARVs are aimed at the disease itself, they are also one of the best forms of palliation, as alongside providing healthy food and other health care, they can enable children with HIV to do all the things children usually do. Taken every day, and with good adherence, ARVs can keep the amount of HIV in a child's body low, so that the CD4 cells remain strong and fight infections, including the HIV. However, for ARVs to work well they must be given every day, usually at the same time of day, and the poorer the adherence the more likely the child is to become sick. It is also important that children continue to take their ARVs even if they are feeling well, as if they stop taking them the HIV may get stronger again and may become resistant to the medication that they

are taking. If this happens, then it may be necessary to change the medication that they are taking which may have more side effects and be more expensive.

ARVs work in different ways against HIV and so a combination of medicines is usually given. Whilst the management of children on ARVs is outside the scope of this handbook, it is important to be aware of the different ARVs used and any significant drug reactions that can occur. Usually children on ARVs will be on nucleoside reverse transcriptase inhibitors (NRTIs), non-reverse transcriptase inhibitors (NNRTI) and some on protease inhibitors. Some of these will have drug interactions that can occur in children receiving palliative care, and other co-morbidities such as hepatitis and other opportunistic infections can increase the risk of interaction and adverse effects of medications.

If a child is showing any signs of a drug interaction a careful review of their medication is recommended. Most will be minor, but a few may reduce the effect of both the ARVs and palliative care medications. Some medications used in children’s palliative care can either reduce the amount of ARVs available in the system or increase them – thus either causing treatment failure or toxicity (see Table 3). It is important to ask relatives and caregivers to look out for any side effects and report any to the health professionals.

**Table 3: Drug interaction**

Palliative care medications that can reduce the amount of ARVs in the system	Palliative care medications that can increase the amount of ARVs in the system
Carbamazepine (Tegretol) Rifampin (Rifadin) Phenobarbital Phenytoin Prednisolone Omeprazole Isoniazid	Ketoconazole Itraconazole Erythromycin Fluoxetine Diltiazem Verapamil Clarithromycin Omeprazole Ciprofloxacin Fluconazole Metronidazole Trimethoprim/ Sulfamethoxazole (Septrin) Haloperidol Cimetidine

Different PIs and NRTIs can increase or reduce the effects of some medications used in palliative care – the most potent of which is Ritonavir which can increase the levels of medications in the blood stream thus increasing the likelihood of dangerous toxic effects (Table 4).



**Table 4: Highest risk medications when used with ARVs such as Ritonavir that increase the levels of medications in the blood stream**

Medications	Impact
Tricyclic antidepressants e.g., Amitriptyline Macrolides e.g., Erythromycin Newer antihistamines e.g., Terfenadine Quinine and Chloroquine	Risk of prolonged QT interval and sudden cardiac deaths
Cisapride	Risk of prolonged QT interval and sudden infant death syndrome
Chloral Hydrate Benzodiazepines Methadone	Risk of prolonged sedation and respiratory depression
Rifabutin (Mycobutin)	Ritonavir increases the risk of rifabutin-induced haematological 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

**Table 5: Common opportunistic infections experienced by children with HIV/ AIDS**

Infections
Bacterial Pneumonia Pneumocystis Pneumonia Tuberculosis Lymphocytic Interstitial Pneumonitis Scabies Ringworm Herpes zoster Impetigo Chickenpox Herpes simplex Oral candidiasis Bacterial meningitis Cryptococcal meningitis Tuberculous meningitis Cytomegalovirus (CMV) infection Cryptococcus Toxoplasmosis

This handbook is aimed at symptom control and is not a comprehensive guide to HIV/AIDS care. However, it is important that you know where to go to get more information on the use of ARVs and

the management of the common opportunistic infections experienced by children with HIV/AIDS (See Table 5).

Most countries will have HIV/AIDS Guidelines which include the use of ARVS and the management of opportunistic infections for children with HIV/AIDS and it is recommended that you look at these for further information. If you can't find country specific guidelines, the World Health Organization has also produced some '[Consolidated Guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach.](#)' Opportunistic infections are a cause of many of the symptoms that children with HIV/AIDS will experience and so in treating the infection you will be reducing their symptoms – core to the palliative care principles of treating what you can treat.

## Indicators of a poor prognosis

It is important to be aware of some of the indicators for a poor prognosis for children with HIV/ AIDS to help in terms of decision making. However, ARVs can help bring a child 'back to life' and children whom you have previously thought were at death's door, once started on ARVs can rally and have a good quality of life. There are certain laboratory and clinical conditions that would suggest a poor prognosis in a child and these include:

### Laboratory markers

- CD4 + T-lymphocyte count < 25cells/mm<sup>3</sup>
- CD3 < 15%
- Serum albumin <2.5gm/dl

### Clinical conditions

- CNS lymphoma
- PML
- Cryptosporidiosis
- Severe wasting
- Visceral Kaposi's sarcoma
- Toxoplasmosis
- Severe cardiomyopathy
- Chronic severe diarrhoea
- Life-threatening malignancies
- Advanced end-organ failure.

When talking with a child's relatives it is important to be open and honest with them, explain the severity of a child's condition, but also explain that you cannot be certain how long a child has got to live. You may be able to suggest days, weeks or months but it is usually harder to be more specific than that.

## Infections

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### Considerations when antibiotics are indicated

In general any infection causing symptoms and affecting quality of life should be treated according to general paediatric guidelines. However, for children with life-limiting conditions some extra considerations should be taken into account:

- Generally, the children are on multiple medications. Common side effects of antibiotics such as diarrhoea may lead to less absorption of daily medication and worsen symptom control in other areas, for example seizure control.
- Children with life-limiting conditions have a *significantly* increased risk for colonization with multidrug resistant bacteria due to frequent hospital stays/antibiotic treatments, presence of devices and immunosuppression. A recent study found that approximately 20% of children admitted to a paediatric palliative care unit were colonised with a multidrug resistant bacterium, rising to 60% of children with a tracheostomy. Surveillance swabs for vulnerable children should be considered to guide the choice of antibiotics.
- As in general paediatrics, allergies are a common problem and should be approached following general paediatric guidelines.

### Route of antibiotics

There is increasing evidence in paediatrics that parenteral antimicrobial therapy is overused and that children's outcomes with oral antibiotics are equivalent. Depending on the child's clinical condition it is thus worth considering starting oral antibiotics or alternatively combining 1-3 iv. doses with oral therapy so that the child can be treated at home or hospice rather than in hospital.

Moreover, in a palliative care setting rules may sometimes be bent; for example, it may be possible to prescribe liquid formulations for antibiotics not normally available in liquid form. Hospital pharmacies and traditional retail pharmacies can be very helpful in providing such information. If off-label or off-licence medication is prescribed, remember to discuss this with the parents and record the discussions in the notes to be protected from a medico-legal point of view.

### When not to treat

Depending on where the child is in their life journey and their quality of life it can be defensible not to treat an infection.

Pneumonia is a common terminal event in many children with life-threatening conditions. The question whether to treat with antibiotics can present both the parents and the care team with an ethical dilemma. It is best to sit down and discuss together the pros and cons of antibiotic treatment for this child at this time. If an agreement cannot be reached a second opinion from a colleague or ethics committee may be helpful.

Even in the terminal phase antibiotic treatment may be unavoidable when treatment can be expected to relieve symptoms, e.g., pain relief in acute ear infections or severe tonsillitis. In those circumstances antibiotics can still be prescribed even if the parents and/or child have decided to forego active treatment. It is worth remembering that antibiotic treatment in the terminal phase is unlikely to extend the child's life.

# Intestinal Failure in Children

[139-149]

## Introduction, terminology, and aetiology

Intestinal or gut failure is the reduction of functional gut mass below that needed for growth and electrolyte stability in children. The term usually refers to children with short gut syndrome, paediatric intestinal pseudo-obstructive syndromes, and other rare conditions of the gastrointestinal tract (GIT). The term is also used to refer to children who require >50% of their calories by the parenteral route for >28 days. However, the population of children for whom palliative care teams are usually asked to become involved and for whom professionals most struggle to manage symptoms, is the group with severe neurological impairment (SNI) and severe, progressive and distressing GIT symptoms, leading eventually to failure of nutrition.

Much of the assessment and management approaches also apply to those with Intestinal Failure due to other causes. A more recent definition of this group of patients has emerged from gastroenterology circles, 'Gastrointestinal Dystonia'. This is defined as:

*'Clinical manifestations of distress (pain behaviour, hyper tonicity, retching, vomiting, autonomic phenomenon, abdominal distension) attributable to the gastro-intestinal tract, as diagnosed by a specialist multidisciplinary nutrition team, directly and indirectly related to feeding and bowel habit, where confounding systems distress have been addressed or excluded.'*

Pain originating from the GIT in children with SNI is known to be of high intensity and when accompanied by vomiting, retching, autonomic symptoms, constipation is one of the most distressing symptom experiences seen by professionals. These problems can lead to feed intolerance which becomes recurrent and persistent despite optimal management of other pain sources- such as constipation, gastro-oesophagal reflux disease, spasticity, and muscular dystonia.

Key underlying processes that may be contributing to GI dystonia and resultant nutritional failure include:

1. Treatable GIT conditions – gastroenteritis, pancreatitis, cholecystitis, volvulus, superior mesenteric artery syndrome, adhesions.
2. Uncontrolled gastroesophageal reflux and constipation.
3. Visceral hyperalgesia and sensitisation of the central nervous system following repeated painful stimulus of the bowel due to 1 & 2.
4. Uncontrolled spasticity or muscular dystonia.
5. Autonomic dysregulation.
6. Central pain and emesis due to damage of the somatosensory system and vomiting centres from the underlying cause of severe neurological impairment.
7. Anxiety and distress from prior significant pain experiences which patients who are both young and cognitively impaired, struggle to manage.

Each of these areas requires assessment from a holistic multidisciplinary team including gastroenterologist, dietitian, neurologist, pain/palliative care team, and allied therapy teams where

available. Each may be targets for non-pharmacological and pharmacological strategies of management. The two considerations to medical management are firstly interventions that lessen GIT distention and secondly medications that lessen symptom generation. The former includes alteration in feed type, volume, rate, route. The latter includes medication trials directed at local GIT issues, visceral hyperalgesia, central neuropathic pain and autonomic dysfunction.

## Assessment

Assessment should begin with a full history of the symptoms experienced, as the focus of management will be directed towards the most problematic symptoms. Evaluate for GORD, constipation, pain, retching/vomiting, and autonomic symptoms. Autonomic symptoms include tachycardia, hyperthermia, flushing, abdominal pain, vomiting, bowel dysmotility, constipation, urinary retention, excess salivation, and agitation. Fully evaluate for other sources of pain including spine, hips, dentition, skin integrity, feeding tube site.

Examination should include dentition, throat, ears, feeding tubes, shunt catheters, inspection, and movement of extremities especially hips. Full abdominal examination. Digital rectal examination is usually not appropriate in children.

Pain scales and direct observation should be used to further assess pain/distress where possible as well as exploration of parent/carer factors such as their response to their child's distress and coping.

## Investigations

Investigations may be of benefit including blood assessment of renal, liver function, inflammatory markers, amylase. Abdominal USS may be indicated to look for causes of pain such as stones and pancreatitis. The appropriateness of more burdensome investigations such as endoscopies, impedance studies and barium studies should be considered on a case-by-case basis, weighing up the burden of the procedure against its expected benefit. This should be a joint decision between the family and professional team and child if possible.

## Management

Ensure optimal management of other sources of pain, spasticity, and muscular dystonia. Manage any anxiety the child is experiencing and support the family and carers in responding to, containing, and supporting the child's distress. Please refer to other chapters of this guide for further information on these areas. Assess medications and reduce those negatively impacting GIT motility. Minimise use of anticholinergic medications if possible. When prescribing medications consider absorption of enteral medications. As the condition progresses it is often preferable to use parenteral or transdermal route for medications where possible.

Consider the following management strategies:

### Feeding

- Assess for overfeeding. Children with SNI have a lower energy expenditure and fluid requirement. Dietetic assessment should be conducted. A trial of 30% reduction in feed volume for 3-4 weeks may improve symptoms.
- Standard polymeric age-appropriate formula feed should be first line for children with SNI who are tube fed. Predigested formula and amino acid formulas may improve tolerance in some. Avoid hyperosmolar feeds and consider reduction in osmolality of the feed with dietetic support. Whey based formula can improve cases of GORD, retching and vomiting in some cases.
- Consider blended diet which may improve tolerance, retching, vomiting and reduce gastric aspirates. However, care must be taken to ensure nutritional adequacy and avoid bacterial contamination.
- Consider reducing rate and volume of bolus feeds for those fed by gastrostomy tubes. Smaller more frequent boluses or 'part bolus part continuous feed' regimens may be of benefit.
- Vent gastrostomy tubes.
- Consider periods of gastric drainage each day to relieve symptoms.
- Gastrostomy is the preferred feeding method over long term nasogastric feeding for children with SNI. In those with recurrent vomiting, feed related aspiration, severe GORD or gastroparesis consider jejunostomy insertion as part of a multidisciplinary decision-making process with the child and family.

### GORD predominant symptoms

In those suspected of having resistant GORD as the predominant symptom of their GIT failure, objective investigation may be of benefit. In those who are more fragile they may not. In addition to the above measures including trials of blended diet and whey-based formulas the following may be of benefit:

- Thickening feed.
- Trial of Proton Pump Inhibitor with follow up. If ineffective reconsider the diagnosis where no objective tests have been conducted and discontinue. There are risks associated with long term PPI use.
- Trial of treatment for H Pylori infection or small bowel bacterial overgrowth.
- Consider prokinetics in uncontrolled GORD, not routinely. Examples include Erythromycin, Azithromycin, Domperidone (caution cardiac effects), Metoclopramide (caution dystonic reactions and reduced seizure threshold). Seek advice from a pharmacist before starting due to associated risks of these medications.
- Consider Jejunostomy tube feeding in refractory cases.
- Several studies of low-grade evidence have demonstrated improvement in GORD symptoms in children with SNI using baclofen. This should be considered only under specialist advice.

### Vomiting and retching

The above measures for feeding and GORD may also be of benefit if vomiting and retching is predominant. In addition, consider:

- 2<sup>nd</sup> line prokinetics under specialist gastroenterology, neurology, or palliative care team advice. Examples include Alimemazine, Cyproheptidine, Procalopride.

- Gabapentin or Pregabalin (action via reduced visceral hypersensitivity and management of autonomic responses).
- Antiemetics. Examples include metoclopramide, levomepromazine. Aprepitant may have a role, but evidence is very limited.
- If vomiting is part of a spectrum of autonomic symptoms consider the following under specialist advice: Gabapentin, Pregabalin, Clonidine (available transdermally).

#### Constipation predominant symptoms

- Gastrointestinal failure includes a dysmotile GIT through all or part of the system. In addition to the above symptoms, it may present as intractable constipation leading to bloating, pain, leading eventually to retching and vomiting. Constipation in children with SNI should be managed in line with guidance for children with normal neurology. Please see National Institute of Health and Care Excellence guideline for Constipation in Children available at: <https://cks.nice.org.uk/topics/constipation-in-children/>.
- For children with SNI, erratic bowel habit and loose, watery stool may be due to faecal impaction. If unsure, undertake a disimpaction regimen using enteral laxatives +/- enemas for three consecutive days or until clear and liquid evacuation.
- Active bowel management with suppositories or enemas may be required routinely in children with SNI with difficult to manage constipation.
- For those on high doses of opioid medications consider rotation of opioids to less constipating preparations e.g., Fentanyl, Buprenorphine. Peripheral opioid antagonists may be considered under specialist advice of a palliative care team.

#### Pain and distress

Distress may be due to any of the above symptoms and central factors discussed above. Initial management of pain usually involves optimising management of the above factors and reducing symptom generation from the GIT. This generally means avoidance of regular opioids and anticholinergics as they act to slow GI motility. However, use of these medications on an 'as required' basis may be required for episodes of pain and distress even early in the course of the condition. Care must be taken to ensure a rational approach e.g., generally not using prokinetics and anticholinergics together as they can act in opposition. Once gastrointestinal failure has progressed to the point where symptoms are unmanageable, despite optimising all of the above measures, or when the end of life is approaching, it may be necessary to institute analgesics, anxiolytics, sedatives and possibly anticholinergics is likely to ensure comfort. This is a difficult transition for families and professionals and clear goal setting, good communication, multidisciplinary team working, and management of expectations of all involved is vital. The following analgesics may be considered in a series of therapeutic trials at any point in the condition, ensuring medications are started one at a time, titrated appropriately and discontinued if ineffective after adequate time to assess action.

- Gabapentin, Pregabalin.
- Clonidine (available transdermally).
- Intrathecal baclofen (if appropriate).



- Opioid analgesics (less constipating preparations such as fentanyl or buprenorphine are preferable for background analgesia). Use in line with the WHO analgesic ladder and in reference to other chapters in this publication.

Anxiolytics such as benzodiazepines may be required to manage pain related anxiety and distress related to other symptoms of GI failure. Access to 'breakthrough' analgesics and anxiolytics of sufficient potency and onset and duration of action is vital especially as the condition progresses towards the end of life. Midazolam used at low doses buccally on an 'as required' basis can significantly improve distress during episodes of feed intolerance, have little impact on bowel motility and be rapidly excreted leaving no longer term effects. Clonidine may also be used to provide similar effect. Use of anticholinergic medications such as hyoscine butylbromide and broad acting antiemetics such as levompromazine are especially useful as the endoflife approaches to reduce GI symptom generation and ensure comfort. It is likely that these medications will need to be given via continuous infusion intravenously or subcutaneously at that stage.

### Artificial Hydration and Nutrition

A full discussion of the considerations of using parenteral nutrition are beyond the scope of this chapter. Initiation of parenteral nutrition for short trials may have benefit for some children but it should be started following multi-disciplinary discussion with the family, guided by sound ethical principals. Clear goals of therapy, duration, and expectations for continuing or not need to be defined prior to starting treatment. As children with GI failure approach the end of life, not taking nutrition and hydration is usually part of the natural dying process, and for patients with severely disabling conditions, where their body systems begin to shut down, they may increasingly lose interest in food or drink naturally. This can make assessment of benefits and harms of continuing to provide assisted nutrition and hydration in this stage challenging for families and professionals. It is essential that clear, honest communication between professionals and families is maintained, and a shared decision-making approach employed to determine the most appropriate care.

### Palliative care planning

For many children with intestinal failure, the onset and progression of the condition is part of a broader neurological deterioration that may continue until the end of a child's life. Palliative care is still seen by many professionals as an option only when other disease directed options have failed or been ruled out. This may result in families not accepting palliative care support, delay in adequate management of symptoms, and reduced likelihood that child and family wishes will be met at the end of life. Once the child's condition is recognised as having the potential to be life-limiting, palliative care planning should be started alongside disease directed options.

## Mouthcare

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This is an often-overlooked aspect of palliative care, but correct management can easily enhance the quality of life for a terminally ill child. If a child has reduced or no oral feeds, plaque can rapidly build up on their teeth. Poor oral hygiene will cause soreness and pain, as well as being very uncomfortable. Taking a good history and a thorough examination inside the oral cavity can help to establish the cause of the issue and direct appropriate management.

### Causes of mouthcare issues

- Poor oral hygiene
- Halitosis
  - Poor oral or dental hygiene
  - Necrosis or sepsis in the mouth
  - Severe infection
  - Gastric stagnation
  - Ingestion of food stuffs such as garlic or onions
- Dry mouth from
  - Mouth breathing
  - Dehydration
  - Oxygen that has not been humidified
  - Drugs e.g., opioids, antimuscarinic drugs (e.g., hyoscine), antidepressants and some antiemetics
  - Radiotherapy
- Sialorrhoea (drooling) from
  - Medications - especially clobazam and clonazepam
  - Cerebral Palsy
  - Neurodevelopmental issues
- Mucositis
  - A common side effect of cancer treatments
- Oral candidiasis
  - Secondary to antibiotics or corticosteroids
- Mouth ulcers
  - Traumatic
  - Aphthous
  - Infectious

- Stomatitis
  - Dry mouth
  - Infections including candidiasis or aphthous ulcers
  - Mucositis secondary to chemotherapy or radiotherapy
  - Malnutrition
- Bleeding gums from
  - Haematological cancers
  - Liver disease
  - Clotting disorders
  - Poor oral hygiene

## Management

### Oral Hygiene

- Mouthcare should be provided on a regular basis and is a key part of management for all mouth related problems. This can be done by parents, allowing them to be actively involved in their child's care.
- Teeth, tongue and gums should be cleaned twice a day using a fluoride containing toothpaste.
- Pink sponges dipped in mouthwash or water can be applied to the gums and teeth to keep the mouth moist. This can be particularly useful if the mouth is too painful to brush.
- Chlorhexidine is available as a mouthwash, spray or gel and is used for the management of gingivitis and the maintenance of oral hygiene, especially for those unable to adequately brush their teeth.
- Apply cream, lip balm or soft paraffin to the lips to prevent dryness and cracking.
- Avoid a high sugar diet and use sugar free medications to avoid tooth decay.
- Rinse mouth after vomiting.
- This attention to mouth care will go a long way to maintaining hygiene, preventing some of the complications and aiding the child's comfort.

### Taste disturbance

- Taste abnormalities can be due to decreased sensitivity or number of taste buds, nutritional deficiencies or medications, and can have a large effect on quality of life. Manage this by:
  - Good mouth care and oral hygiene.

- Addressing any issues with dry mouth or infections.
- Referring to a dietician and considering use of tart foods or foods which leave their own taste such as fresh fruit.
- Stopping causal drugs if possible.
- Medications frequently have chemosensory side effects which can affect compliance with medical treatment regimens, especially for children. For example, many have unpleasant bitter tastes. Manage this by:
  - Trying different preparations.
  - Giving medications via NG/PEG if in situ.
  - Hiding the taste by giving the child a drink of milk or fruit juice straight after the medicine.

### **Halitosis**

- Good dental and oral hygiene.
- Gargle/use mouthwash on waking, after meals and at bedtime.
- Modify diet to avoid garlic and onions.
- Treat dry mouth.
- Treat any infections such as oral candidiasis etc.

### **Xerostoma (Dry Mouth)**

- Correct dehydration.
- Use humidified oxygen.
- Review medications and reduce doses if possible. Common causes include antimuscarinics, antihistamines, tricyclic antidepressants and some diuretics.
- Stimulate salivation by sipping cold drinks, sucking ice cubes or pineapple chunks, chewing sugar free gum and ice lollies.
- Artificial saliva products come in various forms including oral lozenges, oral gel, oral spray and pastilles. The spray is particularly effective. Examples include Glandosane<sup>®</sup>, BioXtra<sup>®</sup> gel and AS Saliva Orthana<sup>®</sup>.
- Regular lip care with petroleum jelly such as Vaseline<sup>®</sup> can help prevent dried and cracked lips.

### Sialorrhoea (Drooling)

- Drooling or dribbling can have a significant effect on quality of life causing unpleasant odours and social embarrassment as well as physical issues including dehydration, perioral chapping, irritation and skin breakdown.
- Acute sialorrhoea may be due to infections or inflammation of the oral cavity or dental problems including dental caries and gum disease.
- Medications including anticonvulsants such as clobazam and clonazepam can cause hypersalivation.
- Chronic sialorrhoea can cause severe and persisting difficulty and can be seen in children with physical disabilities such as quadriplegic cerebral palsy or those with specific oral-motor difficulties.
- A multidisciplinary team approach can be useful in managing sialorrhoea with input from speech and language therapists, dentists, occupational therapists and ENT surgeons.
- Conservative management includes: -
  - Addressing dental causes such as gum disease or caries.
  - Routine good oral hygiene.
  - Considering referral to ENT if problems with nasal obstruction e.g., tonsillar hypertrophy.
  - Postural control of head, neck and trunk.
  - If child can wipe their own mouth, the use of sports sweatbands on the wrist can be more socially acceptable. Encourage child to 'dab' rather than wipe so as not to stimulate local salivary glands.
  - Protective clothing such as absorbent neckerchiefs or bandanas can be used for severe or profuse drooling.
  - Use distraction therapy or gloves/splints to prevent the child putting their fingers/objects into their mouths which will help to reduce the stimulation of saliva production.
  - Avoid acidic foods such as lemon juice and vinegar as well as sweet fizzy drinks which can increase saliva production.
- Oral motor exercises
  - Can be useful if the child has a mild-moderate oral dysfunction but requires good cognitive skills and a high level of motivation.
  - Includes the use of tongue and mouth exercises and programmes to improve oral-facial tone and sensory awareness.

- Intraoral devices
  - Can be effective in those with mild-moderate difficulty who have their adult teeth.
  - Includes palatal training appliances which encourage lip and tongue movements to move saliva to the back of the oral cavity.
  - Not suitable for those with severely limited control of tongue movement or epilepsy due to the risk of aspiration and airway blockage.
  
- Medications – the use of anticholinergic medications work by downregulating the specific neurotransmitter ACh which theoretically leads to the reduction in the production of saliva. All medications are used off license for the treatment of sialorrhoea and have the potential of causing other autonomic side effects including dry eyes, constipation and urinary retention.
  - Topical hyoscine hydrobromide patches – a patch is usually placed behind the ear to allow easy observation of any skin reactions.
  - Glycopyrronium bromide eg Sialanar® – can be given orally or via an injection and is often better tolerated than transdermal hyoscine. Start with a low dose and slowly increment. Has a rapid onset when injected and should be given with meals. Can be particularly useful for those with secretions at night.
  - Oral trihexyphenidyl hydrochloride e.g., Benzhexol® is primarily used for dystonic movement disorders. For management in sialorrhoea start with a very low dose and increment slowly. May be particularly useful for those with dystonic movement disorder.
  - Inhaled ipratropium bromide – a medication usually used in the management of asthma but with a ‘side effect’ of drying the mouth. Usually well tolerated and easy to give via nebuliser.
  - Botulinum toxin type A injections (Botox®) can be injected directly into the salivary gland to irreversibly block the release of ACh. Can provide benefit for between 1-6 months with maximum benefit 4-6 weeks post injection. Doses should be kept low and the procedure performed by a specialist. Side effects include thickening of secretions and dysphagia.
  
- Surgical – several different surgical approaches can be used with variable results. Some gain long term benefits whilst others are left with dry mouths, difficulty in chewing and poor oral hygiene.

### **Mucositis**

- Mucositis can cause pain, difficulty swallowing, phonation problems and poor nutrition.
  
- Difflam® as oral rinse or spray can help provide topical analgesia. Other topical analgesic agents include choline salicylate (Bonjela®).
  
- Gelclair® can be used to coat the mouth and act as a barrier and chlorhexidine mouthwash to reduce risk of secondary infection.

- It should be noted that mucositis can cause considerable distress and pain and systemic analgesia should be considered.
- Nutritional assessment for patients with mucositis should be undertaken as reduced intake is very common and nutritional support may be needed.

### **Oral Candidiasis**

- Nystatin works as a topical agent but can be difficult for children to retain the solution in their mouths. Avoid concomitant use with chlorhexidine.
- Miconazole gel is used by local application and has both local and systemic effects. Care should be taken to consider potential interactions with other drugs.
- Fluconazole as a once daily oral agent is reliably absorbed and is a good alternative to topical therapy. Itraconazole can be used for fluconazole-resistant infections.
- Remember candidiasis may extend beyond the mouth and into the oesophagus.

### **Mouth Ulcers**

- Assessment by dentist.
- Use antiseptic mouthwashes such as chlorhexidine.
- Aphthous ulcers can be treated with topical corticosteroids such as hydrocortisone oromucosal tablets. Beclomethasone dipropionate as an inhaler sprayed onto the oral mucosa can also be used but this is an unlicensed indication.
- Topical anaesthetics such as benzydamine hydrochloride (Difflam® spray) can help with pain associated with oral ulcers.

### **Stomatitis**

- Avoid spicy foods, acidic fruit juices and carbonated drinks. Avoid sharp foods such as crisps.
- Drink through a straw to bypass the mouth.
- Benzydamine hydrochloride (Difflam®) can provide local analgesia.
- Use chlorhexidine mouthwash or gel if toothbrushing is too painful and to help to control secondary infection.
- In severe herpetic stomatitis, systemic aciclovir or valganciclovir may be useful for treating oral lesions.

- Angular cheilitis may be complicated with superadded yeast and bacterial infections. These can be treated with miconazole cream or fusidic acid ointment. Hydrocortisone with miconazole cream or ointment can be particularly helpful.

### **Bleeding Gums**

- Tranexamic acid mouthwashes or gauze soaked in tranexamic acid 100mg/mL or adrenaline/epinephrine solution 1mg/ml (1 in 1000) can be applied to the affected area.
- Bleeding from blood malignancies may require platelet transfusions even in the palliative setting.
- Vitamin K may be useful for the treatment of bleeding associated with impaired clotting in liver disease.



## Paediatric fluid & electrolytes management

[162-164]

This chapter starts by detailing the methods for calculating intravenous fluid replacement volumes for an otherwise healthy child, as described in advanced paediatric life support. In the context of end-of-life care, it may not be appropriate to aim for full hydration, as this can increase secretion production and third space fluid retention with potential for worsening symptoms (respiratory, oedema, tissue viability etc). The final paragraph describes the calculation for subcutaneous fluids, which are likely to be appropriate only in the last days of life and can only provide a fraction of 'full maintenance'. In practice the use of non-enteral hydration at the end of life is rare but can be provided through drip-delivered or machine-delivered infusion either subcutaneously or intravenously (via a central venous access device). Where possible, consideration should be given to enteral fluids or feeds via nasogastric, naso-jejunal, gastrostomy or jejunostomy by bolus or via a feed-pump infusion.

Usually, no hydration decision should be taken based on a single parameter (for example, fluid balance alone). The child should be assessed, in a manner appropriate to their clinical context, potentially including BP, heart rate, respiratory rate, capillary refill time, temperature, weight and general condition.

### Normal 'full' 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 based on the amount of fluid required to keep an otherwise healthy child 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.

### Full 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 (<5%)	Moderate (5-10%)	Severe >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 dehydration/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.

### Subcutaneous Fluids (only likely to be used close to end of life)

Overnight subcutaneous infusion may meet baseline fluid requirements and relieve the burden of restricting movement during the daytime. A suitable site with plentiful subcutaneous tissue (e.g., abdominal wall, upper thigh) is preferred, avoiding areas with skin damage. The site should be checked daily and rotated every 48–72 hours. The reduced timeframe compared to other types of subcutaneous site, is to minimise tissue damage and resultant poor absorption. Skin breakdown, line occlusion or displacement, infection, and local oedema are all potential risks associated with subcutaneous fluid use. Subcutaneous fluids can be infused by gravity or pump in any care setting. Roller clamps used to adjust and maintain rates of flow on gravity infusions vary in their efficiency and accuracy and are also affected by patient movement and by the height of the infusion container, which should be 1–1.5 m above the infusion site. The total volume of fluid determined may be initially based on a percentage (e.g., 10%–30%) of standard intravenous fluid maintenance guidance.

The subcutaneous infusion pumps or gravity flow rates are calculated using a formula that requires:

- ▶ The volume to be infused (calculated as a percentage of the child's maintenance requirements).
- ▶ The number of hours the infusion is running over (12 or 24 hours).
- ▶ The drop rate of the administration set.

Infusion pumps can be used, but in a community setting they are rarely used or readily available. Therefore, a traditional drop rate method (using the drip rate formulae) can be considered. The number of drops per millilitre is dependent on the type of administration set used and the viscosity of the infusion fluid. For example, crystalloid fluid (sodium chloride 0.9%) must be administered via a solution set delivered at a rate of 20 drops/ml.

**Calculate the child's maintenance requirement as above.**

**Decide the percentage of maintenance fluids to deliver (start low at 10-20% and titrate towards 30%).**

**Determine how long to run the infusion in a 24-hour period (over 12 or 24 hours).**

Divide the volume required by 12 or by 24 accordingly, to get a rate in mls/hr.

**Determine the equipment to deliver the infusion.**

Either use an infusion pump and run the volume over the required time or use gravity and calculate a drip rate using the drip rate formula.

Drip rate formula:

$$\frac{\text{Volume to be infused (ml)}}{\text{Time in hours}} \times \frac{\text{drop rate (20/ml)}}{60 \text{ minutes}} = \text{drops/min}$$

**For example, in a 25 kg child starting 20% of maintenance, fluid over a 24-hour period.**

Full maintenance = 1600ml = (10 X 100) + (10 X 50) + (5 X 20)

20% of this is 320ml

Over 24 hours this would be 13ml/hr

A drop rate of 20/ml (crystalloid) rounds to 4 drops per minute

## Neonatal

[73, 165-176]

### Introduction

The importance of high-quality, well-integrated perinatal palliative care provision is increasingly being recognised. Perinatal palliative care is an emotive speciality associated with challenges including diagnostic and prognostic uncertainty and the need to constantly evolve in line with developments in perinatal care. These include advances in antenatal diagnostics and provision of neonatal intensive care interventions at lower gestations, as well as changing societal expectations. Family support is key as parents face the devastation of an unexpected, potentially life-shortening diagnosis for their baby at a time which is most often associated with joy and excitement. Together for Short Lives categorises life-threatening and life-limiting perinatal conditions into four broad groups (see Table 1), whilst highlighting the need for holistic and individualised care for babies and their families.

Specialist perinatal palliative care services and structured pathways which promote multidisciplinary team working and shared-decision making can help to provide more consistent, family-centred care. In the case of a potentially life-shortening antenatal diagnosis, advance care planning in the form of individualised birth plans has been found to be valued by both healthcare professionals and families. These can include guidance about stabilisation measures at delivery such as levels of respiratory support (e.g., non-invasive ventilation vs. intubation), admission to neonatal intensive care and comfort care measures. The opportunity to formulate such birth plans can allow families to

communicate their personal values and care goals, honour the life of their baby, regain some sense of control, whilst limiting or avoiding invasive and distressing interventions.

Parallel planning as part of perinatal palliative care is extremely valuable, particularly where the prognosis is uncertain (either antenatally or postnatally). Parallel planning allows families and professionals to be flexible in their decision-making and guided by the evolving clinical situation. As survival for babies with complex medical needs increases, perinatal palliative care services must consider the longer-term care needs of these infants beyond their discharge from the neonatal unit. This includes consideration of continuity of care, family support (e.g., respite services) and planning for future hospital attendances and/or sudden, unexpected deterioration in the community.

In the context of neonatal intensive care, palliative care often involves joint decision-making with the baby’s family around non-escalation or discontinuation of life-sustaining treatments, often referred to as “reorientation of care”. Intensive care interventions such as mechanical ventilation, inotropic medication and muscle relaxation are frequently weaned and stopped as part of this process, whilst treatments promoting comfort, e.g. pain relief and sedation, are continued. This process is distressing for families and, unless rapid clinical deterioration and death is expected, it is important to give families the time they need to spend quality time with their baby before life-sustaining treatments are discontinued. Families should be encouraged to share their wishes for their baby during life and after death, which may include spiritual, cultural or religious rituals e.g. prayers or christening. This can be supported through chaplaincy teams. Memory-making is a crucial component of neonatal end-of-life care which involves supporting parents to build valuable memories to remember their baby’s short but precious life. This can include photographs and videos, taking hand and footprints as well as special memory boxes, which are often provided by charitable organisations. Whilst most babies in this situation will die on the neonatal unit, if appropriate, parents should be given the opportunity to consider end of life care at home or in a hospice setting. Community palliative care and hospice teams may also be able to facilitate care of the baby and their family after death.

Where removal of the endotracheal tube is planned, often referred to as “compassionate extubation”, it is vital that families are counselled that their baby may change colour and take some gasping breaths and reassured that these are not an indication of suffering. It should also be explained that the time taken for a baby to die after extubation can be variable and difficult to predict. Most babies live for only a few minutes or hours, but some survive for days or significantly longer, depending on their underlying condition.

<b>Category</b>  <b>1</b>	<p><b>Life-threatening conditions for which curative treatment may be feasible but can fail</b></p> <p>Involving palliative care services may be necessary when treatment fails or is expected to fail. Following successful curative treatment or clinical stability, there may be no longer a need for palliative care services.</p> <p><i>Examples of conditions: extreme prematurity, congenital heart disease, severe PPHN</i></p>
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<b>Category</b> <b>2</b>	<b>Conditions where premature death is inevitable</b>  Long periods of intense treatment or intensive care provision may be delivered with the aim of prolonging life and allowing some participation in normal activity. <i>Examples of conditions: chromosomal abnormalities, bilateral renal agenesis</i>
<b>Category</b> <b>3</b>	<b>Progressive conditions without curative treatment options</b>  Treatment is exclusively palliative and may commonly extend over many months or years. <i>Examples of conditions: spinal muscular atrophy, mitochondrial disorders</i>
<b>Category</b> <b>4</b>	<b>Irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death</b>  <i>Examples of conditions: severe hypoxic ischaemic encephalopathy</i>

**Table 1.** Categories of neonates eligible for perinatal palliative care. Reproduced from Together for Short Lives. A perinatal pathway for babies with palliative care needs, 2017.

## General principles of symptom management in neonates

Managing pain and discomfort in neonates can be challenging as levels of pain and response to treatment are difficult to assess, particularly in extremely preterm infants. Validated pain scores for babies exist and can help to improve the reliability of pain assessments, however, they remain subjective, and studies suggest that the smallest babies often receive less analgesia due to under-recognition of pain or distress. Whilst babies are unable to verbally express their response to painful stimuli, it would seem a useful starting point to assume that procedures considered painful or distressing for older children and adults e.g., venepuncture would also be experienced as unpleasant by babies. Such interventions are often unavoidable when providing neonatal intensive care, however, when it is recognised that a baby may be approaching the end of their life, the need for ongoing invasive painful procedures should be re-evaluated. In essence, one must consider whether each intervention/test will change management and potentially improve the baby's quality of life. Where, in rare circumstances, it is felt that they cannot be avoided, procedures should be limited, and comfort measures employed to try to lessen their impact. This may include administration of oral sucrose or breast milk, non-nutritive sucking and containment holding.

The route of administration for medication used during neonatal palliative care should be decided considering existing intravenous access devices and the baby's clinical condition. Babies cared for in the neonatal intensive care unit often have central venous access (e.g., umbilical or percutaneous long lines) or peripheral cannulae. For these babies, it is reasonable to administer analgesia and sedation medication intravenously. Where intravenous access is not available, felt to be too invasive or the expected course of the illness is prolonged, other routes should be considered. These include buccal, enteral or subcutaneous medications.

The enteral route (usually oral or nasogastric) is often preferred and most practical in infants with longer-term life-shortening conditions e.g., epidermolysis bullosa. Enteral medication may not be as effective or appropriate in babies with severe structural or functional gut disorders (e.g. intestinal atresia, microvillus inclusion disease) due to poor absorption. Subcutaneous administration is more challenging in extremely preterm infants due to the lack of subcutaneous tissue but can be particularly useful when providing end of life care at home or in a hospice. This usually takes the form of a syringe driver, where multiple medications can be given via a continuous infusion. Neonatal and palliative pharmacists can provide guidance about medication compatibilities and help to optimise administration e.g., by calculating the smallest dilution volume required for the medication. Care must be taken to review the infusion site regularly for signs of swelling and inflammation.

## Pain management

### *Non-pharmacological*

The value of simple, non-pharmacological comfort measures should not be underestimated. These include non-nutritive sucking, swaddling and containment holding, skin to skin/kangaroo care, positioning and temperature control (i.e., not too hot or cold).

### *Pharmacological*

#### Oral sucrose (24%)

- Can be given intermittently alongside other analgesics and during potentially distressing procedures or cares.

#### Paracetamol

- Routes: oral/NG, PR or IV.
- Can be particularly useful if given regularly. Often given as an adjunct to opiate medication e.g., for abdominal pain in necrotising enterocolitis or for wound pain e.g., extravasation injury/bruising post-delivery.

#### Non-steroidal anti-inflammatory drugs (NSAIDs)

- Ibuprofen is less commonly used than paracetamol but can be used in infants for relief of mild pain. Ibuprofen should be avoided in renal impairment and should be given alongside feeds to avoid gastric irritation.

#### Opiates

- Morphine is the most widely used form of analgesia in neonatal palliative care. At higher doses, morphine also has a sedative effect.
  - Routes: oral/NG, IV, subcutaneous.
  - Side effects include decreased gut motility (which can lead to feed intolerance and constipation), hypotension and respiratory depression.



- Intravenous morphine can be given for acute pain in neonates, using a dose of 25-100micrograms/kg/dose (adjusted according to response), up to every 6 hours. (APPM doses).
- Intravenous morphine infusions are commonly used in neonatal intensive care. The typical starting dose is 5-20 micrograms/kg/hour. This can be titrated upwards to achieve adequate pain-relief.
- In ventilated infants receiving palliative care, morphine infusion rates of up to 40micrograms/kg/hour are commonly administered. If the baby remains distressed despite higher doses, an adjunct should be considered e.g., midazolam for sedation. There is, however, no maximum dose for morphine in neonatal palliative care.
- In unventilated babies, intravenous morphine infusion rates are often limited by the risk of respiratory depression. In this group, rates of greater than 10-20 micrograms/kg/hour are rarely used.
- Morphine can be used at lower doses to treat breathlessness (30-50% dose for pain).

Care must be taken when converting morphine dosing regimens to different routes e.g., IV to oral and vice versa. This is due to differences in their relative potencies.

- ➔ IV morphine is twice as potent as oral morphine.
  - ➔ To convert from IV to oral morphine, the total IV morphine dose over 24 hours needs to be doubled (multiplied by 2).
  - ➔ This will give the total daily dose of oral morphine (over 24 hours), which is then divided by 6 to give a 4 hourly dosing regimen.
  - ➔ Breakthrough analgesia (PRN) should also be prescribed to given in between regular doses if required.
- Diamorphine can also be used as an alternative opioid analgesic in neonatal palliative care and is normally given IV or subcutaneously in this context. It can also be used by the buccal or intranasal routes. It is particularly useful for subcutaneous infusions it is more water soluble than morphine. Smaller infusion volumes can be achieved which is particularly important in the smallest babies. Please see formulary for dosing regimens.

## Feeding

Decisions about feeding in the perinatal palliative care context should consider the expected course of the baby's illness and prioritise comfort rather than optimising nutrition. Feeding can be an emotive area for families, as it often considered a core part of a parent's "normal" care-giving role. Parents should therefore be supported and involved in decision-making around the mode and quantity of their baby's feeds.

During reorientation to palliative care, it is completely appropriate to discontinue or not commence parenteral nutrition or intravenous fluids. In terms of enteral feeds, babies receiving palliative care should be allowed to feed orally on demand if they are able to. Preterm infants less than 33-34 weeks gestation have not usually developed the suck and swallow abilities to effectively breastfeed, however, non-nutritive sucking at the breast can provide comfort and important bonding time for baby and mother.

Many babies at the end of life will not be able to feed orally for reasons including medical instability (e.g., if they are intubated and ventilated), prematurity, or their underlying condition (e.g., neurological impairment). In this situation, small, frequent enteral feeds or continuous pump feeds can be administered via a nasogastric or orogastric tube and mothers should be supported to express breast milk if they wish to. Preterm infants on the neonatal unit are often fed at volumes in excess of 150ml/kg/day to promote growth, however, during end-of-life care, it is appropriate to reduce these volumes. Babies can be given feeds at less than half of their normal volume to provide hydration and satisfy hunger, whilst reducing the risk of unpleasant feed intolerance symptoms such as vomiting. Response to feeding should be continually assessed. Where death is felt to be imminent or feeding itself is felt to be contributing towards discomfort e.g., in cases of necrotising enterocolitis, it is reasonable to stop enteral feeds completely. It is important to remember that, whilst withholding enteral feeds, attention is paid towards appropriate mouth care (which can include using expressed breast milk).

### Gastro-oesophageal reflux

Simple reflux, typically involving small milky vomits or possets, is normal in healthy babies and does not require treatment. Troublesome reflux is more common in premature infants and babies with neurological disorders and can result in distress during or after feeds, respiratory symptoms (including apnoeas) and worsening oropharyngeal secretions.

Reflux symptoms can often be improved with non-pharmacological methods including:

- Nursing baby with the head of the cot slightly elevated, particularly during and after feeds.
- Giving nasogastric feeds slowly, either by “gravity feeding” or delivering the milk via a feed pump over 20-30 minutes.
- Giving smaller volume feeds more frequently e.g., every two hours instead of every four hours or continuously via pump.
- Anti-regurgitant formula milks can be considered in term infants e.g., Enfamil AR.

Anti-reflux medications commonly used in babies include:

- Feed thickeners and alginates e.g., Carobel, Gaviscon Infant.
- Proton pump inhibitors e.g., omeprazole, lansoprazole.
- H2 receptor blockers e.g., ranitidine.

Prokinetic medications, such as erythromycin, are sometimes used to treat reflux in neonates. However, evidence supporting their use is limited and there are concerns about more significant side effects in this group. It is crucial that response to any new anti-reflux medication is assessed regularly and, if not proving effective, treatment should be discontinued. Antiemetics are not generally recommended in neonates. For some infants, a trial of transpyloric feeding via nasojejunal tube can be beneficial in improving troublesome and distressing reflux symptoms.

### Constipation

Constipation can be unpleasant for babies and is more common in those requiring long term opioid treatment. Lactulose syrup titrated to response can be helpful (starting dose 2.5ml twice daily). Ensuring adequate hydration when taking laxative medication is important so, if possible, fluid volumes can be increased.

Acute, distressing constipation in babies can be relieved by administering a “chip” of a glycerine suppository rectally (it is easiest to slice a small chip off a 1gram suppository with a blade).

### Sedation

It is important that sedation is used as an adjunct rather than an alternative to analgesia. For babies that remain unsettled or distressed despite adequate pain relief, sedative medications can be helpful. These include:

- Chloral hydrate: can be given enterally or rectally up to 4 times a day (see formulary for doses). Has a prolonged half life in neonates so can accumulate if used regularly. Can cause gastric irritation, so advice is to give alongside feeds if possible.
- Midazolam: buccal midazolam can be given to help relieve acute agitation or breathlessness (unlicensed). A reasonable starting dose for buccal midazolam is 50-100micrograms/kg. Midazolam can be given as an intravenous infusion, often as an adjunct to morphine. It can also be given subcutaneously, often as part of a syringe driver during end-of-life care. Midazolam is particularly useful in end-of-life care if seizures are contributing towards agitation.

### Seizures

Seizures are relatively common in the context of neonatal palliative care. Causes include hypoxic ischaemic encephalopathy, structural brain abnormalities, metabolic disturbance and neonatal epilepsy syndromes. Seizures can be unpleasant and distressing for the baby, as well as upsetting to witness for those caring for them, including families and healthcare staff. Not every seizure must be treated, particularly if they are infrequent and brief. The decision to treat seizures in the neonatal palliative care context is based on factors including their length, frequency and effect on stability e.g., apnoeas, bradycardias, balanced with the potential side effects of medication and the family’s wishes.

Medication commonly used to treat neonatal seizures include:

Medication	Information
Phenobarbital (Phenobarbitone)	Most common 1 <sup>st</sup> line anticonvulsant used in neonates. Causes sedation and can cause respiratory depression. Loading doses typically given IV. Can be given enterally (usually for maintenance treatment).
Phenytoin	Common 2 <sup>nd</sup> line anticonvulsant. Loading doses typically given IV. Can be given enterally. Can cause skin and blood disorders with prolonged use.
Levetiracetam	Alternative 2 <sup>nd</sup> or 3 <sup>rd</sup> line anticonvulsant. Loading doses typically given IV. Can be given enterally.
Midazolam	2 <sup>nd</sup> or 3 <sup>rd</sup> line anticonvulsant. Often given as a continuous IV infusion for resistant seizures in ventilated infants (due to the risk of respiratory depression). Can also be given subcutaneously. Buccal midazolam is rapidly absorbed and can be given for breakthrough seizures where there is no IV access (unlicensed <3 months age).

### Excessive oropharyngeal secretions

Many babies with neurological problems have difficulties clearing secretions from their mouth and upper airway. These can often be managed with appropriate positioning to facilitate drainage and gentle oral suction. Some babies require frequent oropharyngeal suction which can cause trauma and be a significant care burden for families. Medical treatments include hyoscine hydrobromide patches (typically quarter of a patch, applied behind the ear, changed every 72 hours) and glycopyrronium bromide (usually given enterally). Medication must be titrated to ensure that a balance is achieved between reducing the volume of secretions whilst avoiding overly thick, sticky secretions that are difficult to clear/suction. These medications can also cause a dry mouth and therefore regular mouthcare should be undertaken. In some cases, where medicines have not helped and death is not felt to be imminent, referral for botulinum toxin injections to the salivary glands can be considered.

### Organ donation

The availability of organ donation in the neonatal period has progressively increased in recent years. For some families, the opportunity to donate their child's organs or tissues can bring some comfort, however, this is an extremely sensitive area which must be approached thoughtfully. Organ donation should only be offered to families if an appropriate multidisciplinary team is available and there is a realistic prospect that their baby's organs will be suitable for transplant. Currently, the only solid organs that can be transplanted are the kidneys and tissues such as hepatocytes and heart valves (in babies > 2.5kg). Neonatal health professionals should be aware of their local resources and contacts within their organisation, such as transplant coordinators, so that they can offer appropriate counselling to families.

### Post-mortem

When a baby's death is expected, a post-mortem examination is not usually considered compulsory. However, it is recommended practice to offer a medical post-mortem to all families of babies that have died, even when the cause of death appears obvious. This should be discussed sensitively soon after the baby's death. A medical post-mortem can be particularly helpful in diagnosing underlying genetic conditions, which may have implications for the wider family, including future pregnancies. Some deaths must be reported to the coroner who may request a postmortem if, for example, it was unexpected. Local policies and procedures must be followed in these circumstances and the family kept informed throughout this process.

### Summary

Delivering high quality perinatal palliative care requires a strong culture of multidisciplinary team working, sensitive communication and collaboration with families. Advance Care Planning and parallel planning can help to ensure that babies with life-shortening conditions receive appropriate care and minimise distressing or invasive treatments. Symptom management can be challenging in this group of patients, not least due to the difficulties in assessing pain. The above guidance is a starting point but is not comprehensive. This is a complex and challenging area of paediatric palliative care and therefore neonatal professionals should be willing to seek advice from specialists and local services including children's hospices.

# Neurological

(References see specific text)

## Epilepsy [177]

### 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 [178, 179]

- Correctly diagnose the type of epileptic seizure [179, 180].
- 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 [179].
- 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 [181, 182].
- 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 [183].
- 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.

<b>Antiepileptic drugs</b>			
Modified from R. Mattson Epilepsia vol 36, supp 2, 1995 [184], [179]			
<b>Drugs</b>	<b>Advantages</b>	<b>Disadvantages</b>	<b>Comment</b>
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-clonic seizures, parenteral formulation	Cosmetic or dysmorphic side effects, saturation kinetics	Another drug of first choice for partial epilepsies, potent enzyme inhibitor
Primidone	Effective for partial and tonic-clonic 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-clonic 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-clonic seizures, infantile spasms	Eye problems, dyskinesias.	Unique mechanism of action.

## Intractable epilepsy

The management of intractable epilepsy[177] is beyond the scope of this manual. However it is worth remembering a few points [179, 185-189].

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

- 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 [63]

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 [59, 190, 191]**

#### 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, parents need to be made aware that some minor seizures may breakthrough and do not necessarily require escalation of treatment.

### Midazolam subcutaneous infusion [59, 190, 191]

- 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 (if no response, 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

A specific form of increased muscle tone (hypertonia) in which one or both of the following are present:

- the resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement.
- the resistance to externally imposed movement increases rapidly beyond a threshold speed or joint angle [192].

### Causes

- Cerebral palsy.
- Brain haemorrhage.
- Brain tumours.
- Hypoxic brain damage.

### Management [193]

- Multidisciplinary and patient centred.
- Physiotherapy and Occupational Health.
- Orthoses.
- Medical.
  - Consider medication if spasticity is causing discomfort or pain, muscle spasms (for example, night-time muscle spasms) or functional disability.
  - Baclofen.
  - Trihexyphenidyl.  
  
Be aware of side effect profile (especially constipation, urinary retention and thickening of secretions).
- Botulinum A injections
  - Consider this when spasticity is impeding function; compromising care and hygiene; causing pain/disturbing sleep.
- Intrathecal Baclofen
  - Consider referral if despite the above management the patient continues to have pain/muscle spasms, difficulties with posture, function or self-care.
- Orthopaedic Surgery

- Consider referral if despite the above management the patient experiences hip migration; poor limb function; contractures compromising skin hygiene.

## Myoclonus

### Definition

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

### Causes

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

### Management

- Identify cause where possible.
- Opioid rotation.
- Sodium Valproate (not for girls/young women of child-bearing potential).
- Levetiracetam [192, 194].

## Chorea

### Definition

Chorea is defined by the presence of abnormal, involuntary, continuous, random movements.

### Causes

- Rheumatic fever.
- Neuro-degenerative disorder.
- Encephalopathy.
- Metabolic disorder.
- Drug-induced:
  - Haloperidol
  - Phenytoin
  - Phenothiazines [195]

### Management

- Identify cause and treat appropriately.

## Dystonia

### Definition

Involuntary, sustained, or intermittent muscle contractions that cause twitching and repetitive movements, abnormal postures or both [192].

### What can mimic Dystonia?

- Other causes of high tone:
  - Abnormal muscle contraction (Spasticity or rigidity).
  - Changes in soft tissue property (which can progress to contracture).
- Other causes of abnormal movement:
  - Chorea – ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragment (unlike dystonia NOT associated with postures).
  - Athetosis - slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture (unlike dystonia NOT associated with posture).
  - Stereotypies - repetitive, simple movements that can be voluntarily suppressed (unlike dystonia CAN be voluntarily suppressed).
  - Tonic seizures – usually brief episodes of posturing, with limbs in full extension or flexion, which may occur in sleep (in dystonia consciousness is typically retained, and there is a different patterning of posture. Dystonia also typically disappears in sleep)

### Why Treat dystonia?

Can cause pain/distress, interfere with daily cares, interfere with function and participation. At the extremes, can obstruct the airway, or otherwise contribute to cardiorespiratory compromise.

### What causes dystonia?

Dystonia is a disorder of the central nervous system. It is often associated with impairment of basal ganglia dysfunction but can arise because of disruption to a much broader motor network across the brain. Dystonia is NOT a diagnosis in and of itself. There are many causes of dystonia, including cerebral palsy, other forms of acquired brain injury, neurodegenerative disorders and rarer genetic forms.

### How should you approach treatment of dystonia?

- Preventative measures to reduce the development of triggers for dystonia - e.g., vaccination, good skin care, good nutrition.
- Treatment of triggering/exacerbating factors – e.g., management of constipation, good pain relief, treatment of concurrent infections.
- Medications to directly treat dystonia. Choice depends on background condition, current medication and speed of treatment required.

### **What Dystonia triggers should be considered?**

A top to toe approach is recommended, e.g., at the head – headaches or dental issues. Consider contribution of problems with secretions, constipation/urinary retention or other sources of abdominal pain, orthopaedic issues (spine and hips in particular).

Emotional distress/discomfort may be a powerful driver to dystonia and should be considered and addressed whenever seeing a child with worsening dystonia. Environmental measures such as reassurance or repositioning may prevent the need to give additional medications.

### **What Medications can be used to treat dystonia?**

Acute/Temporising medications (typically working through sedative effect):

- Clonidine.
- Benzodiazepines (e.g., diazepam, midazolam).
- Chloral hydrate (with caution as off license).

**NB** all these medications may cause excessive sedation/respiratory compromise, with an additive effect between them. The minimum doses of each medication should be used, with the maximum interval between doses, for the shortest duration possible. Indications for use should be clearly documented, and frequently reviewed. PRN medications should be under the supervision of an appropriately experienced named Consultant clinician.

Longer term antidystonic medications:

- Trihexyphenidyl – caution with frequently encountered anticholinergic effects.
- Baclofen – with additional role in treatment of spasticity - can exacerbate low truncal tone and excess salivation.
- Gabapentin – with additional role in treatment of pain – can cause excess sleepiness and contribute to respiratory compromise in conjunction with other sedative medications.
- Levodopa – more limited role in children with specific enzymatic deficiencies. Can cause excess vomiting/nausea.

## **Akathisia**

### **Definition**

Motor restlessness, in which the patient feels compelled to pace up and down, or to change body position frequently [196].

### **Causes**

- Drugs including Haloperidol and Prochlorperazine [197].

### **Management**

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

# Nausea and Vomiting

[5, 198-209]

Nausea and vomiting are common symptoms in paediatric palliative care and can cause children and families much distress. There are many causes which may occur in combination to affect children.

Vomiting is mediated through several neurochemicals interacting with receptors which in turn can be affected by the higher cortical centres (e.g., anxiety, memory, and emotion). All these mechanisms ultimately travel through neural pathways to the vomiting centre in the brainstem, triggering the vomiting action via the vagal nerve. Considering the likely causes and underlying physiology in any child will help to target and block the pathways leading to the vomiting response.

## Causes

- Gastrointestinal: e.g. stasis secondary to neurological disease or malignancy. Intestinal obstruction secondary to malignancy or constipation. Mucosal damage secondary to chemotherapy, radiotherapy, or malignancy.
- Drugs: Opioids, antibiotics, NSAIDS.
- Biochemical: Lactic acidosis in mitochondrial & metabolic disease. Renal failure. Lactic acidosis. Hypercalcaemia.
- Infection.
- Raised intracranial pressure: Brain metastasis, blocked intracranial shunts.
- Pain, anxiety, and fear.

## Assessment

- Distinguish between vomiting, reflux and hypersalivation.
- Assess how the child is affected? Individuals may tolerate one or two episodes of vomiting a day, whilst continuous nausea may cause more distress.
- Consider the presence and impact of nausea separately to that of vomiting. Whilst this may be challenging in the non-verbal child, it can be the cause of much misery and is easily overlooked.
- Review medications that may be emetogenic.
- Identify and manage correctable factors e.g, pain, infection, biochemical abnormalities, constipation and gastro-oesophageal reflux.
- Consider the impact of anticipation.

## Management

### 1. Non-pharmacological

- Avoid strong smells – e.g., perfumes.
- Remove leftover food swiftly. Offer small meals frequently if tolerated.
- Acupressure wrist bands (sea bands) may be helpful for some.

- Address any supratentorial contributing factors such as anxiety and psychological distress.

## 2. Pharmacological

- Target anti-emetics to the likely cause, through an understanding of the mode of action and neurotransmitters involved. Most anti-emetics block one or more receptors, though none block all.

### Anti-emetic drug choice

Cause	Drug choice	Action
Drugs, toxins or metabolic (e.g. hypercalcaemia) – stimulate the chemoreceptor trigger zone.	Haloperidol Levomepromazine	Dopamine antagonist, blocks the Chemoreceptor trigger zone pathway. Broad spectrum acting at multiple levels.
Gastric stasis	Metoclopramide Domperidone	Vagal sympathetic: acts peripherally on the gut to improve gastric emptying. Vagal sympathetic: similar to metoclopramide but does not cross the blood brain barrier and therefore less likely to cause extrapyramidal side effects.
Chemotherapy	Ondansetron Dexamethasone Aprepitant	5HT3 receptor antagonist blocks emetogenic action at the chemoreceptor trigger zone & medulla oblongata. Reduces permeability of chemoreceptor trigger zone and blood brain barrier to emetogenic substances and reduces GABA in brainstem. Neurokinin receptor-antagonist: Licensed for chemotherapy induced nausea and vomiting but some reports of use in the paediatric palliative care population.
Radiotherapy	Ondansetron Haloperidol	As above.
Raised intracranial pressure ( Tumour / blocked shunt)	Cyclizine Dexamethasone	Medulla oblongata. As above.
Bowel obstruction	Cyclizine, Hyoscine butylbromide / Octreotide*	As above. Antisecretory antimuscarinic. Reduces peristalsis.
Vestibular (vertigo or travel sickness)	Cyclizine Hyoscine	As above.

Many of the drugs used will overlap in their site of action. If the first-choice drug is ineffective or only partially effective after 24 hours review the dose and consider adding in a second antiemetic.

If you need to use more than one anti-emetic, then make sure they are complementary e.g. Cyclizine and Haloperidol, and not antagonistic e.g. Cyclizine and Domperidone.

In persistent vomiting the oral route may not be appropriate in the first instance. Consider IV, Subcut or rectal routes.

Levomepromazine acts at multiple receptors and can replace other combinations. It will cause sedation at higher doses.

**Steroids** can be useful short term or in pulses by reducing inflammation and oedema. Longer term use should be avoided as risks can outweigh benefits.

\***Octreotide** has been used in adults for vomiting secondary to obstruction but its benefit in children is unknown. As it dries secretions it will worsen underlying constipation.



# Pain: tools for evaluating pain

[148, 210-224]

## Introduction

Rational prescribing of analgesia often depends on having some way of assessing pain. The severity of pain is, for example, one of the three factors that determine the correct dose of opioid (the other two being the patient's physical state, particularly his or her weight, and prior exposure to opioids).

Pain, however, is a subjective experience. Although it is associated with observable physical changes such as tissue damage from injury or illness, there is no consistent connection between the degree of damage and the severity of pain that it causes, and no meaningful comparison can be made between different individuals' pain experience. It is the responsibility of those caring for children to gather as much evidence as they can to help them infer accurately what the child is experiencing. Children who are verbal can often express that directly, and then the emphasis needs to be on exploring their subjective experience. Many children needing palliative care, however, are either pre-verbal because of their age, or non-verbal because of cognitive impairment. The fact that a child is cognitively unable to express the nature and severity of their pain must never be taken to imply that they are incapable of experiencing it; even newborn infants experience pain in much the same multidimensional way as older children and adults.

For such non-verbal or pre-verbal children, parents and clinicians often have no choice but to infer what a child is feeling from observing the way in which he or she behaves. A child can communicate his or her own experience of pain using non-verbal behaviour patterns which those caring for the child must interpret. Such observations of 'body language' are not as reliable as the child's own report would be, were they able to give it. They are, however, far preferable to relying on observation of physiological parameters, such as a raised heart rate, which can be associated with a wide variety of subjective experiences other than pain.

Conventionally, pain scales are considered under three headings: self-report, observational and physiological.

## Self-report scales

The simplest way to invite a child to self-report pain severity is to ask them to assign it a number out of ten. It is important to 'anchor' their response by specifying that zero should represent no pain at all, and that ten should be taken as the worst pain the child can imagine. That anchor does not allow valid comparison of scores between different children, but it does mean that changes in an individual child's score can reasonably be taken to correlate with changes in their own pain experience.

A pictorial analogy for pain and its severity can reinforce a child's understanding of what is being asked. Typically, such visual analogue scales (VAS) are based on a horizontal line or a vertical 'ladder'; again, anchored at 'no pain at all' at one end, and 'worst imaginable pain' at the other. Most such scales translate the child's response into a numerical score which can be easily recorded and tracked as it changes over time. A refinement of the VAS is to use analogies for pain intensity that children find engaging and fun to use, such as poker chips and colours, some of which can even be run as apps on a phone. The most widely used rely on diagrams or photographs of children's faces. A smiley face at one end represents 'no pain', while at the other a distressed crying face represents the 'worst imaginable' pain and there are intermediate grades between them. It is important to note that the expressions worn by faces in these scales are not depictions of the child's own face but rather analogies for pain that represent what they feel. Otherwise, the scale would be prone to inaccuracy when it came to assessing chronic or persistent pain, or pain in children who might not identify with the gender or ethnicity of the pictures in front of them.

VAS only evaluate one dimension of a child's experience of pain, usually its severity. Descriptive self-report measures, on the other hand, allow the verbal child to say much more about the nature of his or her pain and how unpleasant he or she finds it. That can capture aspects of pain experience that might be relevant to how clinicians decide to treat it. A well-validated example is the Pediatric Pain Questionnaire. One highly sophisticated measure of pain combines observation of a child's behaviour patterns with his or her self-report to allow assessment of both severity of pain in the present moment and of its 'chronicity'; the extent to which the child has become resigned to persistent pain.

## Observational

There are several barriers or difficulties when assessing pain in children; children often do not express their pain in the same way as adults and may use play as a distraction, which may be interpreted as their not being in pain. They may also deny or hide their pain to shorten their stay in hospital, and a child's response to pain can be influenced by cultural background, previous experience of pain and biological factors such as sleep deprivation. Assessing children who have complex needs and/or developmental delay presents an additional challenge. These children are at a higher risk of experiencing pain, and particularly in experiencing more severe pain.

Observational pain scales have been devised to help assess a child's experience of pain whatever age or developmental stage they may be; more recently these have been adapted to enable the assessment of pain for children with disabilities.

The FLACC (faces, legs, activity, cry, consolability) scale was designed for children up to age 8 (figure 1). Children should be observed for a minimum of 1-2 minutes if awake, and 2 minutes if asleep. It is one of the most widely used observational pain scales around the world and can be used by families as well as health care professionals. The newer revised r-FLACC has been adapted to be used with children with cognitive and/or physical impairment up to the age of 18 (figure 2), but in addition there is the Paediatric Pain Profile (PPP) which was designed for children who are severely

to profoundly neurologically impaired. Parents are more familiar with their child(ren)'s normal behaviour than healthcare professionals and their input should be sought, particularly in children with disabilities.

## Physiological measures

Physiological parameters can also be utilised to help gauge a patient's pain experience. They involve monitoring:

Heart rate, blood pressure, respiratory rate, oxygen saturations.

These are not particularly useful in isolation as they can be influenced by other biological factors such as sepsis, hypovolaemia, respiratory tract infections, and by fear and anxiety.

In children up to age 1, including neonates, the N-PASS (neonatal pain, agitation and sedation) scoring system can be used for both ongoing pain and acute procedural pain. This utilises a combination of observational and physiological parameters (figure 3): irritability, behaviour, facial expressions, limb tone and vital signs (16), and with any infant <30/40 weeks scoring +1 for gestation, owing to their dampened physiological response.

## Things to remember

Pain scales must be developmentally appropriate. Children with mild to moderate cognitive impairment may be able to use self-report scales and should be given the opportunity to do so.

Pain scores are only applicable for that moment in time and continual reassessment is necessary.

Pain scales are less useful in chronic pain than acute pain.

Listen to parents/carers as they know their child best.

## Summary and conclusion

The child under six years old is often characterised as 'pre-operational'; unable to quantify, abstract or symbolise. Since those are the cognitive skills needed to interpret pain as an analogy, it might be expected that young children would be unable to use any self-report scale. In practice, that does not seem to be the case, and even very young children have often been able to use self-report scales. While many children under six will require an observational approach, before deciding that is necessary there is little harm, and potentially considerable benefit, in offering all children the opportunity to self-report.

For those who are unable to engage with self-report measures, including neonates and some children who are cognitively impaired, a range of tools is available to help the clinician infer the nature and severity of his or her pain. Some such assessment, however approximate it might need to

be in practice, is essential in ensuring that children with life-limiting conditions receive analgesics of a type, and at a dose, that is appropriate for the pain they are experiencing.

**Figure 1:** The FLACC (faces, legs, activity, cry, consolability) scale designed for children up to age 8

	0	1	2
<b>Face</b>	No expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
<b>Legs</b>	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
<b>Activity</b>	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arches, rigid, or jerking
<b>Cry</b>	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
<b>Consolability</b>	Content, relaxed	Reassured by occasional touching, hugging, or "talking to"; Can be distracted	Difficult to console or comfort

**Figure 2:** Revised r-FLACC has been adapted to be used with children with cognitive and/or physical impairment up to the age of 18

	0	1	2
<b>Face</b>	No expression or smile	Occasional grimace or frown, withdrawn, disinterested; appears sad or worried	Frequent to constant frown, clenched jaw, quivering chin; distressed looking face; expression of fright or panic  Individualized behavior described by family: _____
<b>Legs</b>	Normal position or relaxed; usual muscle tone and motion to arms and legs	Uneasy, restless, tense; occasional tremors	Kicking, or legs drawn up; marked increase in spasticity; constant tremors or jerking;  Individualized behavior described by family: _____
<b>Activity</b>	Lying quietly, normal position, moves easily; regular rhythmic breaths (respiration)	Squirming, shifting back and forth, tense or guarded movements; mildly agitated (head back and forth, aggression); shallow, splinting breaths (respirations); occasional sighs	Arches, rigid, or jerking; severe agitation; head banging; shivering (not rigors); breath holding, gasping, or sharp intake of breaths; severe splinting  Individualized behavior described by family: _____
<b>Cry</b>	No cry (awake or asleep)	Moans or whimpers, occasional complaint; occasional verbal outburst or grunt	Crying steadily, screams or sobs, frequent complaints; repeated outbursts; constant grunting  Individualized behavior described by family: _____
<b>Consolability</b>	Content, relaxed	Reassured by occasional touching, hugging, or "talking to"; Can be distracted	Difficult to console or comfort; pushing away caregiver; resisting care or comfort measures  Individualized behavior described by family: _____

Figure 3: N-PASS (neonatal pain, agitation and sedation) scoring system

Assessment Criteria	Sedation		Sedation/ Pain	Pain/Agitation	
	-2	-1	0/0	1	2
<b>Crying Irritability</b>	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation No signs of pain	Irritable or crying with breaks Can be comforted (consolable)	High-pitched or silent-continuous cry Cannot be comforted (inconsolable)
<b>Behavior</b>	No waking up to stimuli No movement	Wakes up minimally to stimuli Little movement	No sedation No signs of pain	Restless, squirming Wakes up often	Arching, kicking Constantly awake or wakes up minimally No movement (not sedated)
<b>Facial Expression</b>	Mouth is relaxed No expression	Minimal expression with stimuli	No sedation No signs of pain	Any pain expression intermittent	Any pain expression continual
<b>Arms and Legs Tone</b>	No grasp reflex Limp (flaccid) tone	Weak grasp reflex Decrease in muscle tone	No sedation No signs of pain	Occasional clenched toes, fists or fingers spread out (splay) Body is not tense	Continual clenched toes, fists, or fingers spread out (splay) Body is tense
<b>Vital Signs: Heart Rate, Respiratory Rate, Blood Pressure, Oxygen Saturation (SaO<sub>2</sub>)</b>	No change with stimuli Hypoventilation or apnea	Less than 10% change from baseline with stimuli	No sedation No signs of pain	Increase 10-20% from baseline SaO <sub>2</sub> 76-85% with stimuli - quick increase	Increase greater than 20% from baseline SaO <sub>2</sub> less than or equal to 75% with stimuli - slow increase Out of sync/fighting vent

# Pain

[8, 225-276]

## Introduction

Pain is one of the most prevalent symptoms in children requiring palliative care support. It is also one of the most feared by parents. A child in pain can be a very distressing experience for everyone: child, parent and professional alike. Fortunately, in most cases, pain is not difficult to manage. Most 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. 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).

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. 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 key to success.

Pain is a 3D film not a 2D picture. Behind the 'scenes', there is a lifelong 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. What children think, what they do and what they might sense or feel, deeply influences their pain experience. The combination of situational factors (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. 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 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.
- Adolescents particularly may underreport pain due to "fear" of what this may represent (e.g., disease recurrence or progression for patients with cancer).
- Cultural beliefs and associations often impact pain experience e.g., patients from Asian cultures often demonstrate stoicism in response to pain; a correlation between the strong cultural values around self-conduct.
- In some cultures, enduring pain at the end of life may be viewed by patients and families as a virtue to be "rewarded" after death.

- Some Buddhist patients and families may decline strong analgesia which may cloud the mind near death.
- 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 it. 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. It is vital to educate 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.

The latest initiative from the World Health Organisation (WHO), 'WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illness' 2012 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 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.

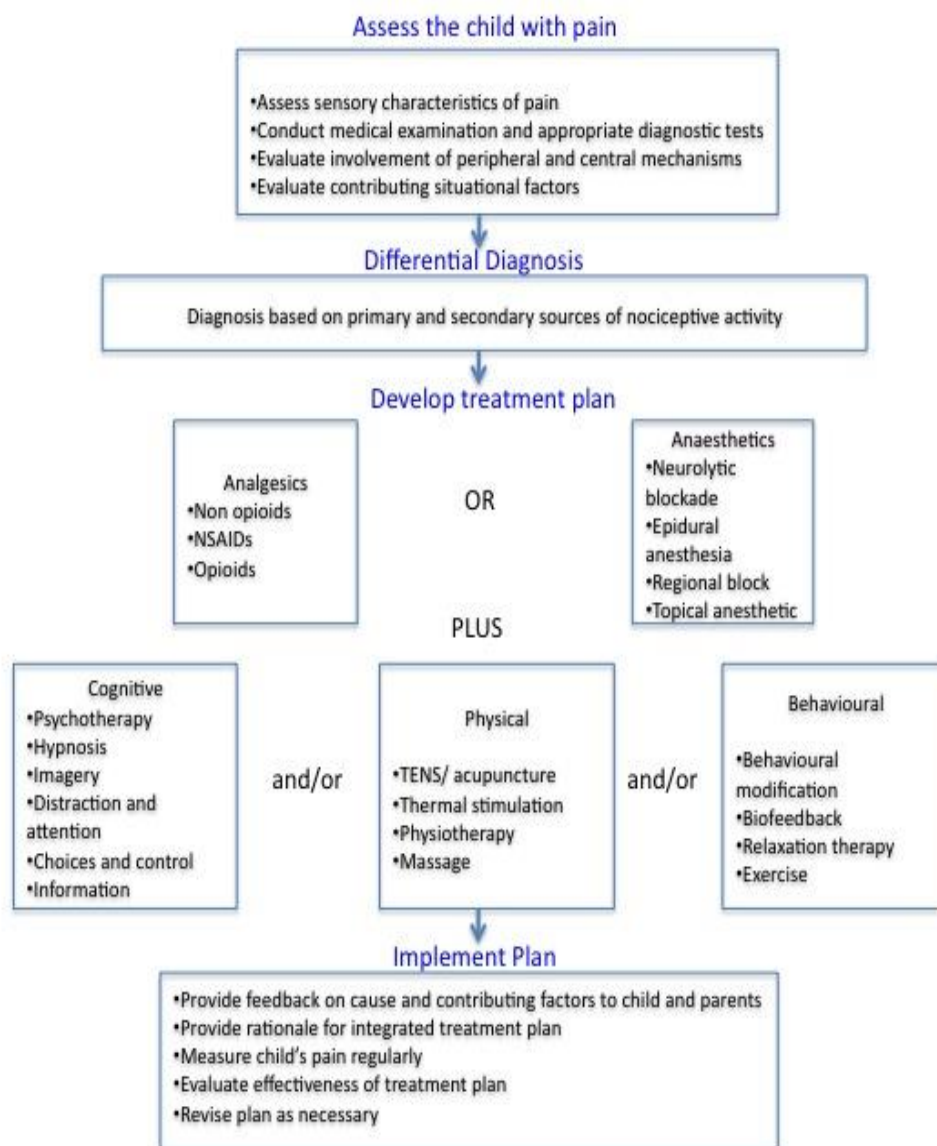
## Pain Management

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 it. Integrating cognitive, behavioural 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 (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 can block incoming pain signals at the level of the spinal cord. 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 (although now withdrawn but still relevant) 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”).

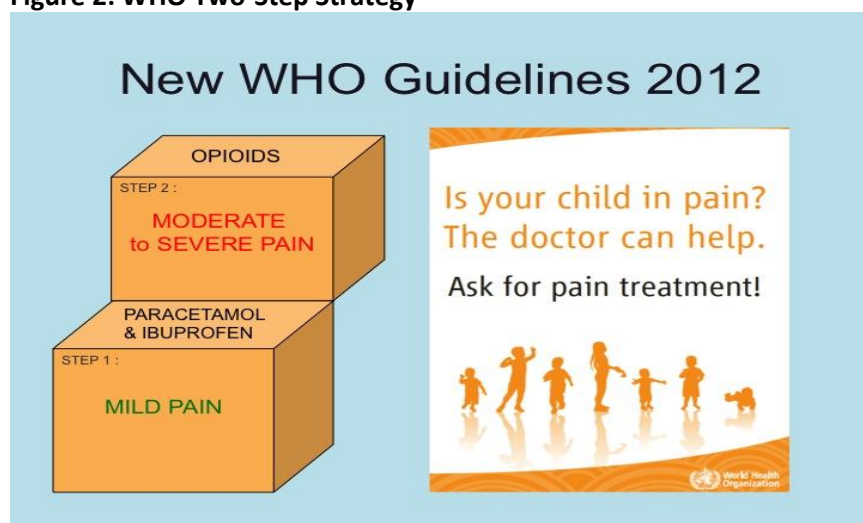
### Using a Two-Step Strategy

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 centred 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’.

Figure 2: WHO Two-Step Strategy



## Step one: Mild Pain

### Non-opioids

#### 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

- Is a safe and familiar medication used frequently in children, though should be avoided in infants under 3 months of age.
- Risk of renal, gastrointestinal and cardiovascular side effects 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, or those still receiving myeloablative chemotherapy.

## 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 may be physiological, psychological or both. Psychological dependence involves a strong desire to take a drug for its psychoactive properties (rather than analgesic properties),

continuing with its use despite potentially harmful consequences or giving a higher priority to drug use than to other activities and responsibilities. Physiological dependence is an anticipated physiological phenomenon brought about by on-going opioid therapy over a period of time and manifests as patients experiencing withdrawal symptoms when the drug is ceased.

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. In fact, there is some evidence that improved pain relief in children and adults with advanced disease not only improves quality of life but may also improve survival time. Additionally, 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 based on the needs of 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 behaviour 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  $1/5^{\text{th}}$  to  $1/10^{\text{th}}$  of the total daily dose, however, historical practice has been based upon adult palliative care prescribing and calculated as  $1/6^{\text{th}}$  of the total daily dose of opioid. The benefit of a lower breakthrough dose ( $1/20^{\text{th}}$  -  $1/10^{\text{th}}$ ) 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. Immediate release opioid should not be administered to children when asleep however (e.g., via nasogastric tube or gastrostomy).
- Slow release (long acting) opioid may be more beneficial for children who require opioid “around the clock” i.e., 4hourly.
- 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. This excludes opioid that is administered prior to a planned and predictable movement such as physiotherapy or mobilising for the toilet (i.e., opioid administered for “incidental pain”).
- 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 and can then be titrated to effect.
- 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, unconsciousness, 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

<b>Figure 3: Opioid Side Effects</b>	
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) occasionally. 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 close monitoring and specialist pain and palliative care knowledge and skill. 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. Adjuvant analgesics may be of particular benefit in the treatment of children with neuropathic pain, dysautonomia and visceral hyperalgesia.

In 2012 the WHO 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.

As is often the case, most data for this heterogeneous group of medications are derived from adult studies, with reference to neuropathic pain conditions. There are readily available, comprehensive systematic reviews of neuropathic adjuvants however, including robust data on number needed to treat (NNT) and number needed to harm (NNH) published by Finnerup et al.

Also, no recommendation was made regarding the risks or benefits of ketamine or systemic local anaesthetics 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.

It is sometimes helpful to discuss this with parents and carers, particularly when prescribing medication off license or off label as it can cause anxiety (therefore it can be helpful to obtain informed consent for the use of these medications and avoid medicolegal implications).

However, when faced with the symptoms of very sick and dying children, many of these adjuvant medications are trialled with anecdotal benefit to patients being 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 area of practice.

### Ketamine

Ketamine is used commonly as an analgesic in emergency medicine, and as a co-analgesic in the peri-operative setting. It may also be prescribed as an adjuvant therapy for patients with acute pain that is opioid resistant, as an opioid sparing agent to those with complex cancer pain, to facilitate opioid weaning and in the management of certain chronic non-cancer pain states under specialist supervision. In addition, there is increasing interest in its use in the paediatric setting.



Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, blocking excitatory glutamate in the central nervous system. It was developed in the 1960s as an anaesthetic agent but has analgesic action at subanaesthetic doses due to NMDA receptor antagonism in the brain and spinal cord. Activation of the NMDA receptor leads to amplification of pain signals, the development and maintenance of central sensitization, and opioid tolerance.

Ketamine has anti-nociceptive properties. It reduces hyperalgesia and has been shown to reduce or reverse opioid tolerance. Ketamine further modulates the effects of numerous pro-inflammatory mediators.

Ketamine can be administered via multiple routes. Perhaps most common are the intravenous and subcutaneous routes, but it can also be administered orally, intranasally or transdermally. While ketamine may be administered spinally, there is a high risk of neurotoxicity and thus no NMDA receptor antagonist is approved for neuraxial administration in humans [28].

Ketamine does not cause respiratory depression and does not have any adverse cardiovascular effects. Its anti-nociceptive, anti-hyperalgesic, anti-inflammatory properties as well as its interactions with opioids and beneficial effects of opioid tolerance mean that ketamine is an important drug for pain management.

Ketamine's use in the peri-operative setting is well documented in the literature. Adjuvant treatment with ketamine both to improve analgesia and reduce post-operative opioid requirement is common.

Adjuvant ketamine peri-operatively may also be beneficial in those patients with opioid tolerance, dependence or substance use disorder [28].

Ketamine is also widely used for management of pain related to cancer, particularly that which does not respond to multi-modal analgesia with opioids and other drugs such as paracetamol, and anti-neuropathic adjuvants such as anti-depressants and anti-convulsants. A 2017 Cochrane review determined that ketamine improves the effectiveness of morphine in treating pain due to cancer.

Neuropathic or mixed pains are often difficult to distinguish from each other, both for patients and clinicians alike. Consequently, although current data in the PPC setting remains scant, ketamine, either as a monotherapy or in combination, may be an effective therapy for the treatment of mixed or neuropathic pain that is not responsive to first-line therapies. Indeed, ketamine has been used in the treatment of opioid-resistant neuropathic pain in paediatric end-of-life care for more than 15 years. In this context it is safe, generally well tolerated and may prevent further dose escalation or facilitate dose reduction, from often already high dose opioid therapy.

Ketamine may be administered as a continuous IV/ SC infusion, as a PCA (patient-controlled analgesia) with background and bolus doses, or orally. Data published in the adult literature demonstrates that ketamine is safe and effective in the out-patient setting; an important consideration for clinicians working in palliative care. The most common indication for ketamine PCA initiation is escalating pain resulting in increased opioid burden, or pain that is refractory to high dose opioids. That ketamine may stabilise opioid requirements is particularly advantageous to clinical practice, as high dose opioid monotherapy is often associated with side-effects.

Ketamine is a drug with an overall favourable safety profile and clinical efficacy, as supported by a growing number of studies. Although some limitations in these data (taken from settings outside of PPC and of limited quality), ketamine may be advantageous in the management of refractory mixed or neuropathic pain in patients receiving palliative care support. Consideration of its use should be on a case-by-case basis, according to the specific pain diagnosis, and dosage and route of administration should be tailored to individual patient needs.

Further information on ketamine dosing may be found in the monograph section of this manual.

### Combination Pharmacotherapy

Combinations of medication are often useful in clinical practice, especially where there has been only a partial response to maximum tolerable doses of a single drug. The theoretical rationale for drug combinations is often difficult to support empirically because of the challenges running pharmacological studies in the small population of children needing palliative care. Hypothetically, pain relief can be enhanced through combining pharmacologic interventions to target different receptors along the nociceptive pathway. Opioids, anticonvulsants, non-steroidal anti-inflammatory drugs, and local anaesthetic agents can all relieve cancer pain, which may be complex and combine bone, deep tissue and neuropathic elements. A multimodal approach is effective in relieving difficult pain.

## 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., mucopolysaccharidosis, 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 tumours 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 intervention, 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 oesophageal 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, managing 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 nervous system. Neuropathic pain in children can be exceptionally severe and disabling. It is a particularly challenging diagnosis in children due to heterogeneity of conditions, diagnostic uncertainty and unknown trajectories. Recognition and diagnosis based on clinical history and "positive" signs and symptoms (e.g., paraesthesias, spontaneous pain, hyperalgesia – exaggerated response to normally painful stimuli; allodynia – pain elicited to non-painful stimulus), or "negative" signs and symptoms (sensory loss and numbness) is challenging.

If possible, 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', or a difficulty to describe pain at all should be a signal that there is a neuropathic component to the pain, particularly if occurring in the context of a biomedically (or anatomically) plausible disease or lesion of the somatosensory nervous system.

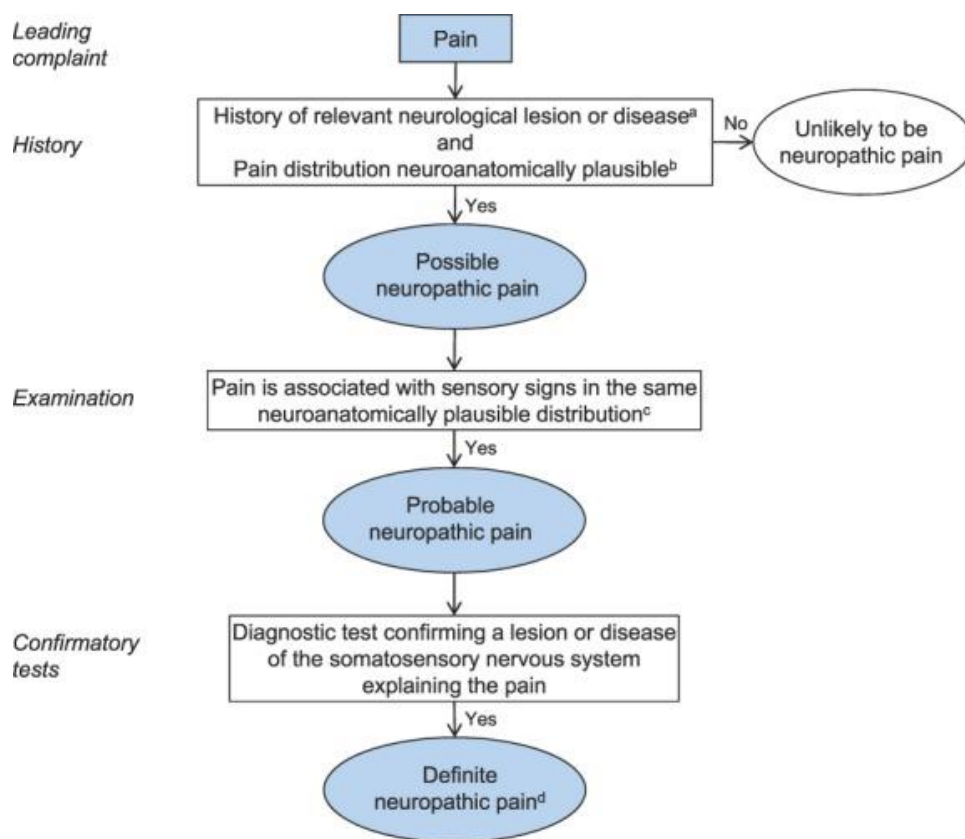
In adult practice assessment and diagnosis is more rigorous, with amongst other things, the presence of pain with a distinct sensory distribution in a corresponding body part, indication of

sensory signs within the area and confirmation of the lesion by a diagnostic test. 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.

Well documented causes for NP in children include: - Post-traumatic, or post-surgical nerve injury, phantom limb pain, genetic /metabolic diseases (e.g., Fabry’s disease), some chronic infections (e.g., HIV/ AIDS), cancer and chemo-radiotherapy.

**Figure 4: Treatment algorithm for neuropathic pain (NP)**



*Open access permission, original cited from Finnerup, N.B. Neuropathic pain: an updated grading system for research and clinical practice. Pain, 157(8), p.1599.*

Prevalence of chronic pain with neuropathic features in adults is estimated to be 3.3% - 8.2%. Prognosis for recovery from neuropathic pain in the adult patient population is often poor. Evidence suggests that prevalence in the paediatric population is much lower, and that prognosis is improved.

The paediatric nervous system has a greater degree of plasticity, which is likely to account for the improved restitution of function and lower incidence of pain than is seen in adults.

Historically, treatment for NP in children has been “off-label” with the anticonvulsant drug gabapentin. Gabapentin is an  $\alpha$ -2 delta ligand, whose action at selective voltage-gated calcium channels in the central nervous system and dorsal horn of the spinal cord has an acute inhibitory effect on the release of excitatory neurotransmitters, including glutamate and substance P. It has been used in the management of paediatric neuropathic pain for more than 2 decades and is widely considered first-line therapy. Gabapentin is generally well tolerated in children, with a relatively low adverse effect profile. There is a lack of significant drug interaction, but caution should be taken in patients with renal failure and doses adjusted according to glomerular filtration rate.

Pregabalin, a similar drug to gabapentin may also be used in the treatment of neuropathic pain, but this is generally prescribed less frequently than gabapentin, and much less frequently than is the case for adult patients. Clinicians should be aware that a significant side effect of pregabalin is depressed mood and suicidal ideation. Caution is advised in prescribing pregabalin for adolescent patients.

Should there be a contraindication to gabapentinoids, a commonly prescribed alternative for paediatric neuropathic pain is amitriptyline, a tricyclic anti-depressant. Amitriptyline exerts its analgesic effect by inhibiting the re-uptake of noradrenaline and serotonin, thereby enhancing descending inhibition. Its most encountered side effect is somnolence, and therefore it is often prescribed for patients with neuropathic pain and disturbed sleep. It is generally well tolerated and efficacious for neuropathic pain. It can however be associated with a prolonged QTc interval, and therefore clinicians should be mindful when prescribing amitriptyline for patients treated with multiple drugs which may be associated with QTc prolongation, such as ondansetron or haloperidol. An electrocardiogram may be warranted prior to commencing amitriptyline in such cases.

Newer, atypical opioids such as tramadol and tapentadol have also been prescribed for neuropathic pain in adults. Each have activity at the  $\mu$ -receptor, but also influence descending inhibition through inhibition of serotonergic (both tramadol) and noradrenergic (tramadol and tapentadol) re-uptake. Neither tramadol nor tapentadol are licenced for paediatric use. Tramadol has been prescribed “off-label” however in some paediatric institutions.

### Cannabinoids

In recent years, much attention has been garnered internationally around the use of cannabis-based products for medicinal use as a therapy for pain control, among other symptoms (e.g., nausea, spasticity and appetite stimulation). Indeed historically, cannabis has been used to relieve pain since Egyptian times. However, contention exists surrounding the efficacy of these products and the legal, ethical and societal implications associated with their use including safe prescribing, administration, and dispensing as well as quality and constituents of product.

The social and political climate continues to evolve, along with changes in the regulatory environment for its use in Western countries which has included scheduling from a “prohibited” to a “controlled” substance in Australia, rescheduling to an unlicensed product prescribed by specialists in the United Kingdom and minimal regulation in Canada and some States in the United States of America.

Such changes have been brought about both by political direction as well as continued public demand.

The opinions of advisory groups such as the International Association for the Study of Pain, and Faculties of Pain Medicine both in the United Kingdom as well as Australia & New Zealand are virtually one and the same; that while cannabis products for medicinal use may have “potential for therapeutic use”, the product safety and efficacy is not yet established. Moreover, there is continued concern in relation to the incidence of adverse event in cannabis users, particularly young people which include respiratory impairment, cognitive dysfunction as well as psychotic disorders.

A recent systematic review of medical cannabinoids in children and adolescents concluded that there is currently insufficient data to support their use in neuropathic pain. Cannabinoids interact powerfully and potentially dangerously with a wide range of medications that children with life-limiting condition are likely to be taking. As enthusiasm for the possible benefits of cannabinoids continues to outstrip available evidence for their safety and efficacy, many families are choosing to self-medicate with cannabinoid products. Clinicians should be aware of the potential toxicity of drug-to-drug interaction between cannabinoids and opioids.

It is generally accepted that the current evidence base regarding the efficacy and safety of medicinal cannabis products fails to reach the threshold at which either the IASP or faculties of pain medicine listed above can endorse their general use for pain management.

## 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 group of patients including central pain and visceral hypersensitivity (see below).

Classical symptoms in an infant or nonverbal 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, these symptoms 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. 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.

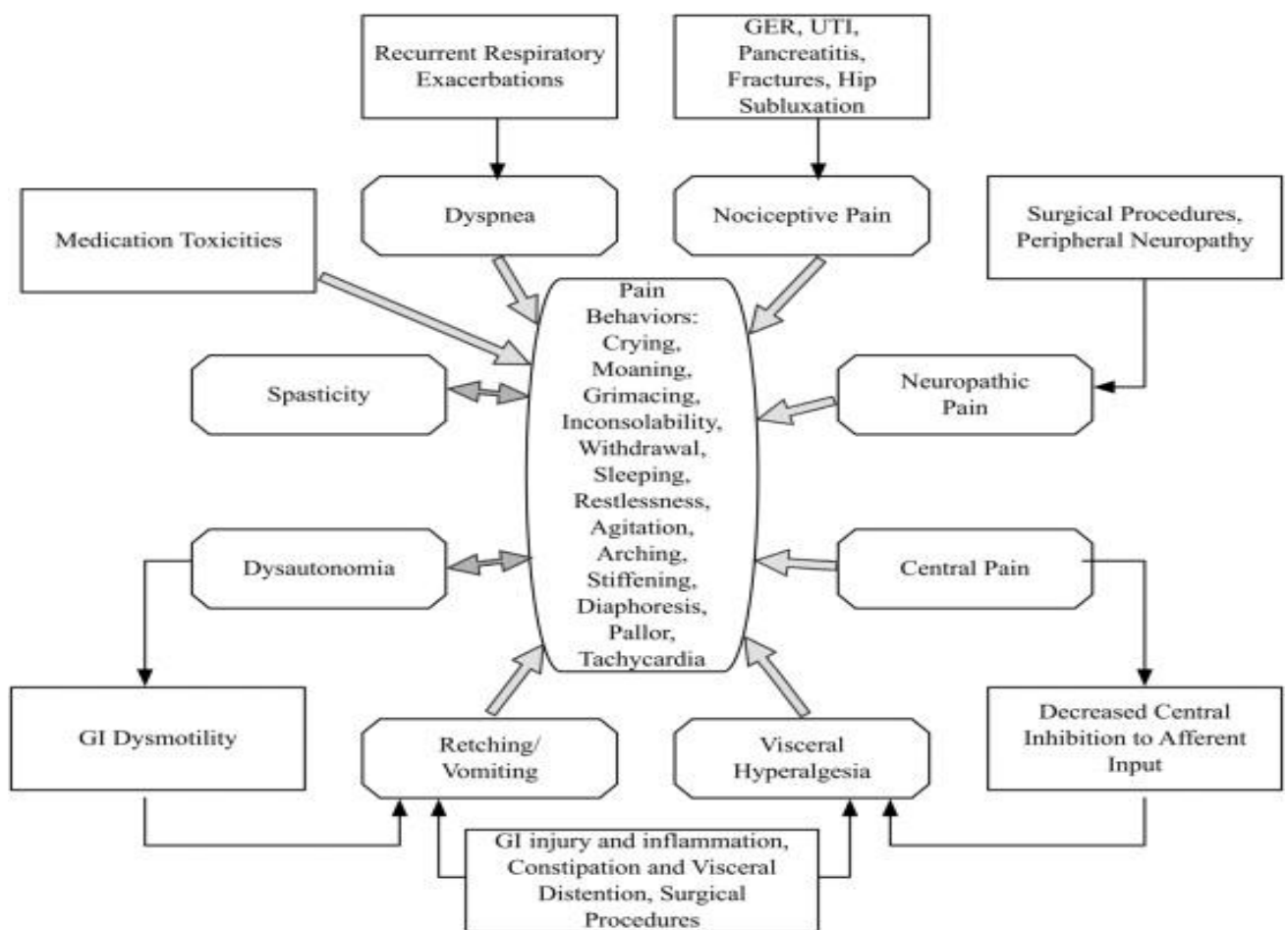


Figure 5: Sources of Pain Behaviours in Children with Severe Neurological Injury (with permission)

## 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. 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 irritability'. However, it is usually a diagnosis of exclusion and 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.

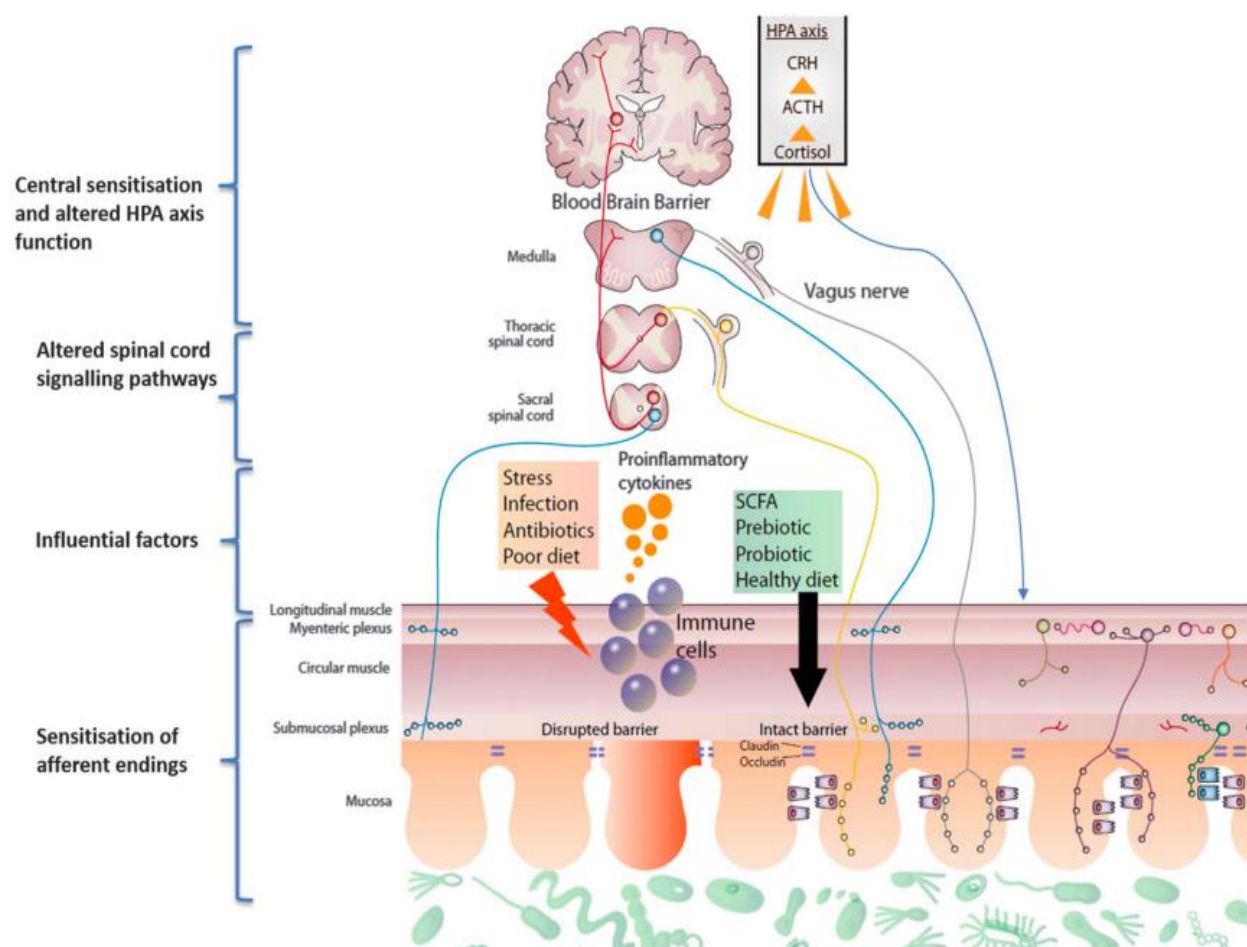
## Visceral Hyperalgesia

Visceral hypersensitivity or hyperalgesia is an altered response to visceral stimulation resulting in activation of pain sensation. Caused by an up-regulation in gastrointestinal sensory input, a hallmark of visceral hyperalgesia is usually painful organ function. 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. 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, vomiting and spasmodic pain are frequently seen despite adequate treatment of constipation and gastro oesophageal reflux. In recent years, a growing body of evidence has emerged regarding the role of the gut microbiota in the bi-directional communication along the gut-brain axis. This delicate balance may be disrupted by factors such as stress, antibiotic exposure in early life, depression and constipation, which in turn affect visceral nociceptive pathways.

There is no diagnostic test for visceral hyperalgesia, but on examination, patients with hyperalgesia of abdominal viscera may have an area of cutaneous hyperalgesia or allodynia over the abdominal wall.

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.





**Figure 6:** \*Diagram and accompanying text reproduced from “The gut microbiota as a key regulator of visceral pain” O’Mahony, S.M et al PAIN 2017 Apr (with permission).

## Cancer pain

Pain is a common and often distressing symptom of cancer, as reported by both children and their parents. Much like their adult counterparts, pain in children with cancer can occur because of the disease burden itself and its treatments.

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 trialling 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, such as steroids (e.g., oral dexamethasone). 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.

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 hyperalgesia (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, with increasing doses of opioid (i.e., pain typically worsens, as doses of opioid medications are increased). It is thought to be due to adaptive (neuroplastic) changes in the central and peripheral nervous system. Typically, OIH presents as pain distinct from the site of disease (often widespread, rather than localised), and is accompanied by hyperalgesia (an increased response to painful stimuli), allodynia (a painful response to a normally non-noxious stimulus), or both. In the setting of OIH, pain characteristics are often different to those that were observed at the original presentation.

Distinguishing OIH from clinical entities such as opioid tolerance, progressive disease, opioid withdrawal, addiction or pseudo-addiction is a critically important skill for clinicians.

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.

OIH can be extremely distressing for patients and their families. Its treatment, somewhat counter-intuitively, requires reduction in opioid burden. Considerable diagnostic confidence, along with a therapeutic rapport is required to reduce the opioid consumption in a child with end stage cancer. It is therefore recommended to switch the opioid if possible, and dose reduce by ~20 %, potentially in combination with an NMDA receptor antagonist. Methadone has been reported to have efficacy in reducing high dose OIH.

### **Management of Opioid Induced Hyperalgesia (OIH).**

Clinical evidence of OIH arose mainly following observational studies of patients treated with long-term methadone, for the treatment of substance dependence. The exact mechanism is not completely understood, but both central and peripheral contributors have been postulated.

Key among proposed central mechanisms is a change to the glutaminergic system. Glutamate is a major excitatory neurotransmitter of the central nervous system, and it is believed to play a critical role in the development of OIH. This is because opioid use, both acute and chronic, increases NMDA receptor activity. Such glutamate-associated NMDA receptor activation, can result in spinal neurone sensitization, thought to contribute to the development of OIH. This phenomenon has been prevented by NMDA receptor inhibition (e.g., through use of ketamine).

Other proposed central mechanisms include release of spinal excitatory pro-nociceptive neuropeptides e.g., calcitonin gene-related peptide (CGRP) and cholecystokinin, and alteration in opioid receptor responsiveness. The latter results from G-protein second-messenger systems being converted from an inhibitory to excitatory-coupled mode. Such alterations in G-protein activity occur following prolonged exposure to opioids and the resultant increase in excitatory activity is thought to be a possible contributor to opioid tolerance and OIH.

A final, peripheral mechanism is thought to involve activation of serotonergic receptors, which may shift the balance from one of descending inhibitory control to a pro-nociceptive state. Recent rodent models demonstrate that administration of the 5HT<sub>3</sub> antagonist ondansetron can mitigate against OIH.

Early assessment and prompt recognition is key to managing both opioid tolerance and OIH. While there is significant overlap between these conditions, there are important differences in presentation and critically, in clinical management.

One of the key differences is that treatment of OIH usually requires a reduction in total opioid, and therefore an early differentiator may be clinical response to increasing opioid dose. If the patient is experiencing opioid tolerance, analgesia is expected to improve, but if analgesia deteriorates (or pain worsens in the absence of any progressive disease), OIH should be considered.

OIH can be prevented through a reduction in the total opioid burden to the patient. Key to this, is adopting a multi-modal approach to analgesia using co-analgesics, as well as interventional modalities when appropriate. Where appropriate, clinicians may consider a reduction of opioid dose through co-administering anti-depressant or anti-convulsant medications (particularly important if the patient is experiencing neuropathic pain), as well as simple analgesics such as paracetamol and non-steroidal anti-inflammatory medications (NSAIDs).

Interventions such as regional or peripheral nerve blocks, or intrathecal administration of opioid may serve to allow a reduction in systemic opioid, thereby reducing side effects that may otherwise be experienced with escalating doses of oral or parenteral opioid medications.

## Methadone

Methadone is an important analgesic in the management of severe paediatric pain. It is a long-acting, lipid soluble opioid with good oral bioavailability, excellent absorption from the upper GI tract and no active metabolites. It offers several advantages in the management of severe, refractory pain. Its use has been limited by its complicated pharmacokinetics and comparative lack of data in the paediatric patient population, however. It is crucial that clinicians are familiar with methadone and its unique pharmacology in order to provide safe and effective treatment to appropriate patients.

Methadone is a racemic mixture of two isomers: the L isomer is a  $\mu$ -receptor agonist, while the D-isomer is an N-methyl-D-aspartate (NMDA) receptor antagonist. The effects of NMDA antagonism in the brain, spinal cord and peripheral nerves leads to analgesia and reduced hyperalgesia in neuropathic and inflammatory pain states and may also prevent or reverse opioid tolerance.

Methadone has complex pharmacokinetics (long half-life and large volume of distribution), considerable inter-individual variation in response, and a narrow therapeutic index. Genetic polymorphisms in genes coding for methadone-metabolizing enzymes, transporter proteins and  $\mu$ -opioid receptors are thought to explain in part the observed inter-individual variation in the pharmacokinetics and pharmacodynamics of methadone. Cytochrome P450 (CYP) 3A4 and 2B6 have been identified as the main CYP isoforms involved in methadone metabolism. Due to these complexities, close observation is required for conversion to methadone from other opioids, for dose initiation and titration. Conversion to methadone from other opioids is highly complex, and oral morphine equivalent doses vary depending on duration of previous opioid therapy.

Methadone is highly potent at equivalent doses in opioid-tolerant patients. This is a very important consideration, particularly when managing pain in patients with progressive malignancy who may have been treated with high-dose opioid medications.

In adult practice, there are two common strategies for opioid rotation to methadone, but there is no such evidence based in paediatrics. These are summarised below:

- In one approach, previous opioid therapy is stopped entirely, before starting a fixed dose of methadone at variable dose interval.
- The other approach incorporates a gradual transition period where the dose of the former opioid is reduced and partially replaced by methadone which is then titrated upwards.

There is also a strategy that involves augmenting existing pain control with methadone.

High doses may be required for the initial few days while tissues saturate. Consequently, some clinicians may choose to prescribe a “loading dose” of methadone. However, continuing with higher doses may lead to complications such as sedation and respiratory depression or even death due to the “secondary peak” phenomenon.

Methadone is highly potent at equivalent doses in patients who are opioid-tolerant. This should be borne in mind when considering methadone for patients with advanced malignant disease, who may already be treated with high dose opioid for pain.

Methadone is available in oral tablet, liquid or parenteral form. It has good oral bioavailability and excellent absorption from the upper GI tract. For patients who are unable to be treated with oral methadone, parenteral methadone may be administered either subcutaneously or intravenously. Skin irritation may occur with subcutaneous administration and therefore double dilution and regular change of syringe is advised. For further information, see notes on methadone in the drug monograph section of this manual.

### Patient Controlled Analgesia / Parent or carer proxy-controlled analgesia

Pain is a key symptom in children and young people (CAYP) requiring palliative care support, and those with advanced malignant disease. More than 75% of children dying from cancer experience pain, with some children having suboptimal pain control. Comprehensive assessment and multi-modal approach to pain management is therefore crucial to best patient care. Yet despite this, pain is only effectively managed in 30% of patients [29].

Severe pain is most effectively managed with opioid medications. An effective modality for administration of opioids is as an infusion, in the form of patient-controlled analgesia (PCA). PCA for children is widely available in much of the world and is commonly used. It is known to be a safe and effective modality with children as young as five years old able to self-administer “rescue” doses of analgesics for either breakthrough or incidental pain. In addition, a PCA pump allows patients to have some control in the management of their pain, within the safe limitations as prescribed by their clinician.

In those children either too young, or developmentally (physically or cognitively) unable to operate PCA themselves, their parents can manage the PCA by proxy. Reports in the literature demonstrate that PCA by proxy is demonstrated as being safe, with complications or adverse events occurring very rarely.

Portable PCA is possible via a computerised ambulatory drug device (CADD) and the evidence base surrounding their use in the outpatient paediatric setting is increasing. Key benefits afforded to patient care through PCA are flexibility, rapid and effective titration of analgesics and high levels of patient and carer satisfaction. As a result, pain control at the end of life is often superior and may be considered a (good) option for pain management at the end of life in children of all ages, in both in-patient and out-patient settings.

The indications for home PCA may include: -

- 1) Opioid is required for pain management or terminal dyspnoea.
- 2) Opioid medications are required for symptom management, but the oral route is not tolerated.
- 3) Patient or family’s wish to be or remain at home in the context of a clinical deterioration for which the child’s symptoms require management with parenteral opioid.
- 4) Inadequate therapeutic response to oral analgesia.
- 5) Sudden onset, severe breakthrough or incidental pain which does not respond to oral analgesics.

Effective pain management is usually achieved through a combination of a continuous dose of opioid at a basal rate (or so called “background” infusion) and /or interval doses (bolus doses) to manage incidental or breakthrough pain. This analgesic modality provides effective pain relief by tailoring delivery of opioid to specific patient need. PCA may safely be used in both hospital, home and hospice settings.

Generally, opioid requirements increase in the last 2 weeks of life. In the case of patients with cancer, this increase is usually a function of disease progression in the terminal phase and/ or opioid tolerance.

## Interventional Pain Modalities

Pain is one of the most feared consequences of a cancer diagnosis. As is mentioned earlier in this chapter, it can occur as a direct result of disease itself, because of therapy, or both. Parents often report pain as the “most problematic” symptom their children experience during cancer treatment. Effective cancer therapy therefore demands meticulous pain assessment and excellent analgesic management to achieve effective pain control. This is fundamental to preserving function, maintaining and enhancing quality of life, compliance with cancer therapies and potentially survival time.

While most pain related to cancer can be effectively treated with systemic analgesics (opioids – either enteral or parenteral, along with adjuvants if indicated), a small minority of children may have debilitating pain that either fails to respond to escalations in systemic analgesia, or experience dose-limiting side effects (such as sedation or nausea) that preclude further escalation of systemic analgesics. In such instances, it is appropriate first to consider switching to an alternative opioid. However, if this is not possible due to either lack of availability of opioid, or previous treatment with alternative opioids, it may be appropriate if local resource permits, to consider an interventional modality for pain management. It should be borne in mind however, that the proportion of paediatric patients requiring an interventional approach to pain management is far fewer than would be encountered in adult practice.

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 metastases, vertebral fracture) and, depending on local community service support, does not necessarily prevent patients from being cared for in their preferred setting.

### Peripheral nerve blocks

A range of peripheral nerve blocks can be used to treat both acute and chronic pain, but it is important that practitioners are appropriately experienced to perform such blocks. Recent techniques have involved use of ultrasound to identify anatomical landmarks and nerves to be blocked. The duration of the block (and hence the pain relief) can be extended by placing a catheter near to nerves or nerve plexuses to deliver a prolonged infusion.

Nerve blocks may be diagnostic – to locate the source of pain, or therapeutic – to treat pain. Individual nerves or plexi may be blocked. Autonomic blocks may also be performed (e.g., lumbar sympathetic block for lower limb phantom pain).

It is beyond the scope of this chapter to detail specifics of the many nerve blocks that may be employed in the treatment of cancer pain, but there is much published in the anaesthetic and pain literature.

## Neurolytic blocks

A neurolytic block is a longer-lasting form of nerve block. It involves deliberate injury to a nerve, which leads to temporary degeneration of targeted nerve fibres, thus interrupting transmission of nerve signals [4] Neurones]. Neurones are damaged by the interventional practitioner placing a needle close to the nerve and either injecting a neurodestructive chemical agent (e.g., ethyl alcohol or glycerol) or producing damage with a physical method such as cold (cryotherapy) or heat (radiofrequency ablation).

A successful neurolytic block may result not only in significantly improved pain, but also a reduction in the requirement for analgesics such as opioids. There may be serious complications associated with neurolytic blocks however, and thus they are rarely performed other than in patients with a limited life expectancy due to malignant disease.

## Intrathecal therapy

Fortunately, around 90% to 95% of adults with cancer experience adequate pain relief with aggressive pharmacological treatment with opioids and adjuvant analgesics. It is however, important to recognize that 5% to 10% of (adult) patients will require more invasive therapy. This percentage is likely far less in the paediatric population, but nonetheless practitioners working in paediatric palliative care should be aware of indications for more invasive therapies, should the need arise.

Intrathecal (IT) drug delivery is an important consideration for patients who have optimised pharmacological therapies without adequate freedom from pain, or who have intolerable side effects that preclude up-titration of analgesics to therapeutically effective doses. Via the IT modality, analgesia is achieved through direct, continuous infusion of medications into the cerebrospinal fluid (CSF).

Both opioid (e.g., morphine or hydromorphone) and non-opioid (e.g., bupivacaine or clonidine) medications are delivered by an IT catheter. This affords more effective and selective targeting of receptors in the central nervous system. Consequently, patients experience improved analgesia with a significantly lower dose of drug via a more precise delivery mechanism. Further, IT drug delivery is associated with fewer systemic sideeffects with little to no effect on motor function.

IT therapy has been used for intractable cancer pain for more than four decades. The first description of its use via an implantable pump was in 1981 [7]. IT therapy has since become more sophisticated and can be delivered both by an implantable pump, or via an externalised device such as a CADD (computerised ambulatory delivery device) pump which can deliver both a continuous infusion and a bolus dose if required. IT therapy may be beneficial for patients with both mixed neuropathic and somatic/visceral pain.

Extreme caution must be taken when managing patients with intrathecal analgesia and it is best managed by clinicians experienced in its use. For reference, potency of oral opioid to intrathecal morphine is in the order of 100:1 (i.e., intrathecal morphine is between 100 times more potent than oral morphine).

## 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 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 as well as physical symptoms being an indication for the practice of sedation, existential suffering must also be considered in the evaluation of refractoriness of symptoms. 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.



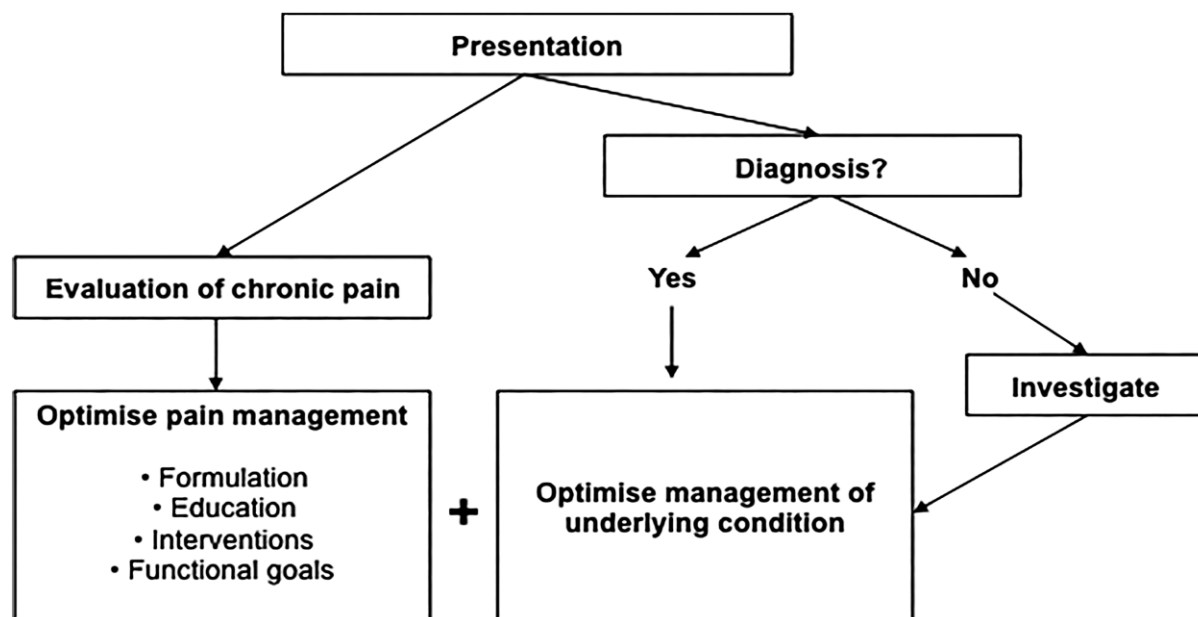
## Pain: Chronic pain

[277-289]

Descartes' 16<sup>th</sup> century image of a man being burned by a hot flame depicts early theories about pain and its role as a biological warning system. At first the biological explanation was that a painful stimulus results in a unidirectional message being transmitted to a distinct part of the brain via the spinal cord, resulting in an appropriate withdrawal motor response. However, this simplistic view does not explain several phenomena:

1. Why does pain occur with no identifiable injury?
2. Why does a small injury, like a paper cut, result in a large pain?
3. Why is the same pain felt differently by different people?
4. Why is the same pain felt differently by the same person at different times?

The current view of pain neurobiology is more complex. Pain perception in nociceptive, inflammatory and neuropathic states is modulated by descending pathways from the brain and are also influenced by genetic, developmental and environmental factors. There is increasing evidence that psychological distress, parental and sociocultural factors influence CNS plasticity which affects pain presentation, related disability and prognosis of disease-related and idiopathic pain disorders. Therefore, the relationship between the initial sensory stimulus and the perceived pain is dynamic and dependant on all these influences. Sleep disturbance, mood disorders including suicidal ideation and functional compromise such as school non-attendance have been more commonly reported by children and young people with Juvenile Idiopathic Arthritis, sickle cell disease, chronic headache and mixed pain states and is related to pain intensity, emotional and psychological functioning. Even when an underlying pathology is known, variability in the associated chronic pain is often independent of disease severity, so it is important to evaluate the chronic pain as a distinct problem. This biopsychosocial model for pain provides a practical formulation guide by which to prescribe an individualised, multimodal pain management plan for children and young people with chronic pain.



**Figure 1:** The clinical management of chronic pain at presentation

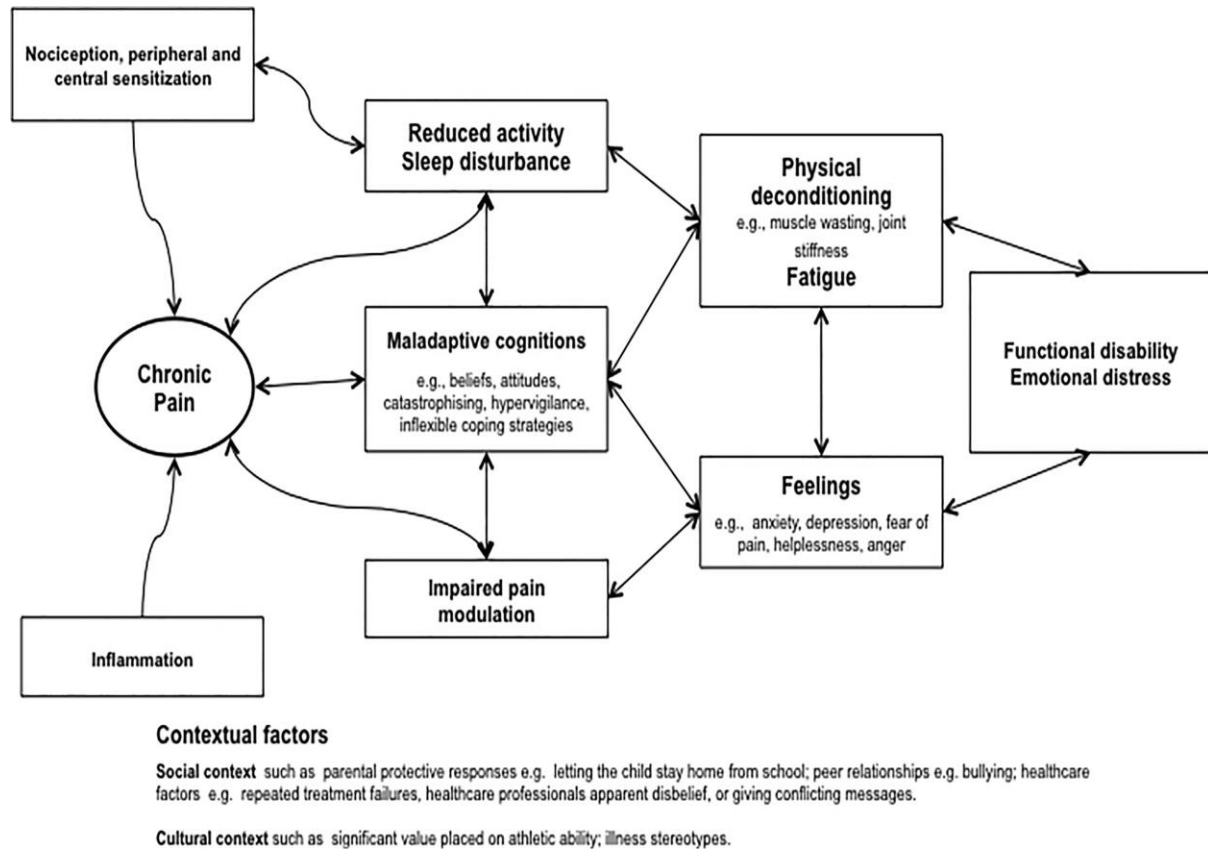
The aim of assessment is to identify and quantify pain mechanisms, behaviours and areas of functional compromise by direct questioning, use of age-appropriate health/pain specific questionnaires, psychological screening and physical examination. Biopsychosocial formulation is discussed with the young person and parents, identifying age-appropriate functional outcome goals that are personal to the young person and family. The resulting agreed pain management plan is monitored and reviewed prospectively with re-formulation as needed. This occurs alongside disease-directed investigation and therapy.

The specific areas for evaluation are:

- Biological - pain characteristics (descriptors, exacerbating/alleviating factors), physical functioning (level of activity), sleep.
- Psychological - mood, cognitions.
- Social - school attendance, relationships and activities, parenting (solicitous, protective), parental characteristics (mood, cognitions).

## Formulation

This is the summation and integration of the knowledge acquired through the assessment of a child and their family. It is an individualised framework, utilising current evidence and theory, for the developmental and maintenance of chronic pain in the child. This describes the pain problem, the degree of emotional distress and functional compromise and provides clarity for subsequent changes to the plan which can be based on re-formulation during monitoring reviews.



**Figure 2:** Generic formulation diagram for chronic inflammatory pain. reproduced with permission from Professor Christina Liossi (professor of health psychology, University of Southampton)

## Pain education

The aim is to provide common ground between evidence-based knowledge and individuals' beliefs about their pain. It provides cognitive reassurance by explanation, educational resources and practical support and may enable young people to engage with pain management plans.

## Interventions:

- Pharmacological interventions**- These should be directed towards the mechanism of pain or presence of central sensitisation, where evidence for benefit is extrapolated from adult studies or acute pain management and on an individualised risk/benefit assessment. These interventions should be instigated as a therapeutic trial in partnership with the child and family.

Pharmacological agent	Pain condition
Paracetamol and Non-steroidal anti-inflammatory agents (NSAIDs)	<ul style="list-style-type: none"> <li>As required in combination or singly in all types of pain conditions but the effect for individuals is variable.</li> <li>Long term use in inflammatory pain conditions but needs monitoring for side effects and efficacy.</li> </ul>
Opioids	<ul style="list-style-type: none"> <li>Rarely indicated or effective in chronic non-cancer pain (except in some palliative care settings).</li> <li>Side effects limit their efficacy and in the long term, tolerance, dependence and opioid induced hyperalgesia may cause further problems.</li> <li>Other effects such as sleep associated breathing difficulties, pathological fractures, immunosuppression, cardiac and gastroenterological issues have been described.</li> </ul>
Amitriptyline	<ul style="list-style-type: none"> <li>Effective in adults with neuropathic pain.</li> <li>Effective in children with neuropathic pain and sleep disturbance.</li> <li>May be effective in some patients with other pain conditions where central sensitisation is thought to be present, e.g., fibromyalgia</li> </ul>
Gabapentin and pregabalin (Calcium channel blocking anticonvulsants)	<ul style="list-style-type: none"> <li>Effective for neuropathic pain in adults and children.</li> <li>Pregabalin is effective for post-chemotherapy neuropathic pain.</li> </ul>

- Psychological strategies** - These interventions have been found to decrease pain intensity and/or frequency in headache and mixed pain states post treatment and at follow up but did not improve depression and anxiety. Cognitive behavioural therapy, the psycho-social intervention which aims to change maladaptive thoughts, beliefs and attitudes leading to unhelpful pain behaviours provides the framework for the interventions below. The aim is to develop emotional regulation and coping strategies.

Intervention	Description
Relaxation	Self-management techniques such as music, distraction, foursquare breathing, guided imagery, mindfulness meditation.
Hypnosis	Hypnotherapists can record implanted suggestions such as “you are going to sleep soundly tonight” which can be played back when needed.
Biofeedback	Feedback about involuntary parameters (heart rate, blood pressure, respiratory rate) which change during pain episodes that can be used to monitor the effect of a pain management technique (e.g., relaxation).
Sleep management	Improvement of sleep hygiene by regular routines, winding down, relaxing and avoiding stimulating food, drink and activities before sleep.
Pacing	Self-directed and balanced periods of activity and rest daily aimed at re-introduction of normal activity gradually.
Operant strategies	Aimed at parents to support functional improvement in their child’s pain behaviours.

- **Physical interventions**

Intervention	Description
Physiotherapy	As part of multimodal pain management, improving tissue healing, functional impairment, mood and prevention of muscle strength deconditioning associated with reduced activity.
Transcutaneous electrical nerve stimulation (TENS)	A low voltage electric current applied to the skin provides a competing sensory stimulus which can be effective for pain management, e.g., musculoskeletal pain
Desensitisation techniques	Application of repeated sensory stimuli such as light touch, pressure to an area of skin which exhibits hypersensitivity and allodynia due to abnormal pain processing. This is done in short bursts of a few minutes gradually increasing from light touch with tissue or cotton bud to strokes and increasing pressure over time as tolerated.
Local heat and cold analgesia	Applying heat and cold packs may be helpful in acute and chronic musculoskeletal pain as they may reduce muscle spasm, metabolic demand and elasticity of connective tissues, as well as reducing delayed-onset muscle soreness (DOMS).
Mirror box therapy	A sensorimotor technique for localised limb pain (e.g., neuropathic phantom limb pain, CRPS) where movement of the unaffected limb is visualised in a mirror obscuring the affected limb. This creates a visual illusion of normal movement of the affected limb.
Complimentary therapies	Acupuncture may be effective in some children with chronic pain.

## Pain: Spiritual

[290-292]

“Spirituality represents something of a conundrum. It is a term both ancient and modern, an anachronism and a contemporary issue. It occupies an increasingly popular space in western culture and yet is shrouded in mystery and ambiguity. Spirituality is to be found at the very foundation of the modern hospice movement, and it receives copious mention in palliative care, but it has no standard definition, practice or policy. There is a paucity of research about spirituality and few claim any expertise. And yet a concern for spirituality is one of the distinguishing features of palliative care, which prides itself in its holistic philosophy”. (The Dying Soul, 2001, p11)

### Introduction

As you can see from the quote above, spiritual care is the proper concern of all those working in children’s palliative care, but it is an area of care we can shy away from. Addressing the important questions around spirituality/spiritual pain is just as important as a child’s ‘symptom management’. Dealing with the spiritual questions will in fact have a big impact on the child’s physical symptom management. (You may want to think about the concept of Total Pain and what you understand by this?).

Dame Cicely Saunders introduced the idea of “total pain,” which included the physical, emotional, social, and spiritual dimensions of distress. These 4 aspects can be thought about by looking at Box 1

Box 1: Total pain

<p><b>Physical:</b> Pain due to disease location Other symptoms e.g. nausea, constipation Physical decline &amp; Fatigue</p> <p><b>Social</b> Relationships with family and friends Role within the family School life</p>	<p><b>Psychological</b> Grief, Depression Anxiety, Anger Adjustment to condition</p> <p><b>Spiritual</b> Existential issues Meaning of life and illness Personal value as a human being Religious faith</p>
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Addressing some of these issues may help us distinguish the different aspects of a child's pain and making the right intervention. This is well expressed by Cole when she reports:

'Sometimes kids report pain that is disproportionate to what is organically going on in the body. You need to show you believe them. Even if it seems far-fetched, there is a truth in what they are telling you'.

We are very good at caring for people's bodies but not so good at caring for their Souls. We can misinterpret spiritual pain as a physical pain and intervene in the wrong way. What you will discover is no amount of medication can take spiritual pain away. I refer to this spiritual pain that cannot be treated with medication as **Soul Pain**. This term seems to capture what we are talking about and can help people who may find 'spiritual' hard to comprehend. Soul Pain is the experience of becoming disconnected and alienated from that part of you that makes you who you are and from the people around you to help give your life meaning, namely your family. Soul pain is something we come to feel, see and sense in another. Soul pain is a pain no nurse or doctor can treat or cure with medication from the CD cupboard!

This approach has grown out of talking and working with parents of life-limited and life-threatened children over many years of clinical practice and sharing that journey with families and other professionals. This section may help you think more creatively about spiritual care and how you can support parents and children when they are having to face difficult and challenging questions around issues to do with 'spirituality'. It may also help you think about a suitable approach when talking with families and their children about their illness, and maybe about their dying and death.

It should be recognised that the issues of 'spirituality' and 'religion' are very important aspects of the care we should be addressing. 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 therefore means that 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 spiritual issues are key issues for any family living with a child with a life-limiting or life-threatening condition who may die whether they are religious or not.

It would be impossible in this short section to answer all the questions you may now have about spiritual care, just as it is impossible to answer for families what are sometimes called the 'Why questions', such as 'why my child' or 'why our family' or 'why now' which can form part of a bigger question around the 'meaning of life'. Nobody can give you answers to these profound questions the family are now confronting you with and that you as a professional may well be asking yourself. They will be different for each family.

What we can offer the family is a way of working with their child. I call this '**Watch, Wait and Wonder time**'. This is a way of sitting with a child and letting them lead the conversation. It is far from easy for anyone to do. Professionals find it hard, as do parents, to sit with the child and try and stay in that difficult place and listen to the child's questions, to hear their fears. It is about making a

journey of discovery with the child. We will not be failing the child by not knowing the answers to some of the questions they may now have. By being open, honest and gentle, not knowing can be a place of strength and may even be reassuring for the child. The aim or task of providing spiritual care is that of co-creating a safe and secure, or what you could call a 'sacred space', where the child can express their inner feelings, suffering, and know that it is alright to do so, that they will be heard and taken seriously. It should also be a space where the parents, siblings and staff can have the freedom to do the same. However, we must recognise that the most we can do is to prepare and hold the space where the miraculous may happen.

I once read a book that was called "Gateway to Hope: An Exploration of Failure" by Mary Boulding which I found very reassuring. 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 the family and child, but the struggle will be worth the investment in the long-term.

This advice focuses on the needs of the child who is ill but is just as applicable to the whole family/team. 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 deep part of us and is always present. Your spirituality cannot be isolated from all that makes you who you are.

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

I have suggested that spirituality is about a 'journey' and that journey is 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 openness and awareness, which is often unique to a child's early years. As we get older this openness and awareness can get pushed to one side.

### **Definition**

Spiritually 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 that world.

In talking about spirituality, we need to bear in mind that we all come from different social and cultural backgrounds, that we each have a past and a future, and it is out of this setting that our spirituality will manifest itself. It is from this background or setting that a child's questions will flow. It may also be in non-verbal communication that they express this inner world.

I have found that children with a life-limiting or life-threatening condition have a 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. Parents can be very well placed to understand them, because they will be able to understand their child's language, play and art far better anyone else. To do this they,



as parents, will need the support of the professionals around them who may have travelled this road with other families and so have some insights to share with them.

### *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? The current situation in which you find yourself will challenge your value systems and notions of spirituality and cause you to reflect deeply. You should know that this process of questioning is not unusual and that you should not feel guilty about it.

Spiritual care is about responding to the uniqueness of 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 their 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 children 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, we need to try and create a safe and secure place, which I have come to call a 'sacred space', where 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 and not your own.

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 children's palliative 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 are responsive to their needs, not the needs we think they may have, or our own needs. Never underestimate a child's understanding of what is going on, not only with their body, but within their inner world. You may be surprised at how your children have 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, dying and death.

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 a 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 and try and **be present** to them and not want to give them **presents**; to try and make it better. We need to learn to listen. We need to be able to "waste time" in order to hear and understand the questions and

desires that are being spoken by the child or the family. We have to listen to understand rather than listening to respond. You could call this the “apostolate of the ear”.

I have come to learn over the years of clinical practice that 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. As T.S. Eliot says, “We shall not cease from exploration and at the end of our exploring will be to arrive where we started and know the place for the first time” (Four Quarters, 1944). He goes on to talk about ‘a condition of complete simplicity’, something children have in abundance. As adults we can overcomplicate spiritual care and so shy away from it, and think it is the business of the ‘Priest’, but this is not the case. At this point in time the child has Chosen **YOU** to share their inner world and you need to have the courage to respond in kind.

Dame Cicely once said that those of us who have spent time in the company of people with mortal illness have learnt from them that we are always challenged to know more and to help more effectively but, above all, to listen. Sometimes there will be no answers to give to those in apparently desperate situations and we find ourselves with nothing to offer but **silent attention**. Another way of saying this is: **Watch, Wait and Wonder** with the child and family in front of you.

So, in conclusion:

- Spiritual care is to be found at the very heart of good palliative care.
- Spiritual care is different from religious or pastoral care, but the two should be seen as complementary.
- Spirituality has an increasingly popular space in western culture and yet is shrouded in mystery and ambiguity.
- Spirituality has no standard definition or practice and will be different for each person or family.
- Pain can be measured, suffering cannot.
- **Soul Pain** (Spiritual pain) is a real symptom that demands all your clinical skills and presence.

# Psychological

[170, 293-303]

The whole subject of child psychiatry in paediatric palliative care is vast and complex. Symptoms that present are often a reflection of the internal stresses and strains within a family.

Given the strong interdependent relationship of psychological symptoms on physical symptoms, and vice versa, management of psychological consequences of illness are as vital as the management of any physical symptoms, in the holistic palliative care of children and their families.

## Parents / Family

Helping parents/family 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.

Many paediatric palliative (and other specialist) teams have specific psychology and counselling support (available to both child and family). With or without this, parents/family may need further specialist treatment about their own psychological state/illness, and it may be appropriate to encourage them to seek further help (e.g., via their General Practitioner). Let them know that to look after their children, that they need to first look after themselves (you could use the airplane safety analogy: 'Put your own oxygen on before applying to your child').

Even without specific psychological support we should not underestimate the benefit of good old-fashioned care and compassion. We need to give families 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 faith leader

## Child / Young Adult under our care

Children themselves also present with psychological symptoms and can be left feeling frightened and guilty about their illness.

In much the same way as described above, children may be helped by being given time to explore their feelings. As well as being therapeutic, this can also highlight /diagnose other specific issues (psychological and physical) that may need to be treated further.

However, one must be aware that childhood development impacts the assessment and treatment of psychological issues and that symptoms manifested by children are not the same as those manifested by adults. A complete understanding of the concept of death is thought to be understood by a child of 8 years old, whilst the concept of the irreversibility and finality of death can be understood by those as young as 5-7. 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.

There are set criteria to clinically diagnose many psychological illnesses such as depression and anxiety disorders, and knowledge of these may fall outside palliative specialist expertise. There are also many that think that a low mood/anxiety is a 'normal' response to the knowledge that they have a life-limiting condition, which may indirectly influence the level of intervention given. It is worth noting that whilst symptoms of grief and depression may be similar, normal grief reactions are self-limiting and are not associated with self-blame or worthlessness, as in depression.

For the difficulties and reasons detailed above, the diagnosis of psychological symptoms in children with life-limiting illness may be under or overtreated.

Fortunately, a child psychiatrist can be very helpful and supportive. Also, it is worth trusting the natural instincts of the parents and carers who often know the children best.

For severe psychological symptoms, such as suicidal ideation, it is **always** necessary to seek help from specialist psychology/psychiatric colleagues.

## Physical Symptoms

It is widely recognised that there is a close relationship between physical and psychological symptoms. Perhaps the most obvious being the compounding and cyclical influences of anxiety, with pain and breathlessness.

Additionally, these relationships can lead to difficulties in diagnosis, where somatic symptoms of psychological illness overlap with that of physical illness (e.g. cancer can lead to anorexia, sleep disturbance, constipation and weight loss - all symptoms of psychological illness).

It is also worth noting that psychological symptoms often compound each other - e.g. anxiety is often associated with depressive symptoms.

For this reason, a good history and open communication can help identify causative or compounding factors/symptoms.

## General approach to the management of psychological symptoms

In the absence of a prompt psychiatric specialist review there are still several management options. This holds true for all symptoms.

### 1. Correct the correctable

- **Review medications** (many medications used in paediatric palliative medicine may contribute to psychological symptoms e.g. corticosteroids, benzodiazepines, antipsychotics, antiepileptics).
- **Optimise management of other potential contributing co-morbidities** (e.g. electrolyte disturbances, withdrawal from medications, cerebral metastases).

- **Optimise management of other potential contributing symptoms** (e.g. pain, breathlessness, insomnia, and other distressing symptoms). See various other chapters within this manual for more help with this.

## 2. Non-pharmacological treatment

As described above, offer appropriate support and the opportunity to talk. The techniques used depending on the development of the child, include: -

- Facilitation of open discussion allowing the child to express worries and fears (evidence exists that withholding information and a lack of communication about death increases fear and anxiety)
- Correct misconceptions
- Develop coping skills
- Distraction techniques
- Offer spiritual support
- Other non-pharmacological therapies such as:
  - o Relaxation therapy
  - o Art, music, play therapy etc

More specialist psychological approaches such as cognitive behavioural therapy (CBT) may also be helpful.

## 3. Pharmacological treatment

If despite our best efforts, and the approach detailed above is insufficient to relieve clinical symptoms of anxiety or depression, we must not be afraid of using medication as an adjuvant.

## Specific pharmacological management of psychological symptoms

### Anxiety

Particularly in the terminal stages, anxiety can be helped with several drugs each of which can have different benefits.

Benzodiazepines such as midazolam, lorazepam and diazepam can be useful in treating short term agitation and anxiety. The fact that they are typically quick acting and can be given in various forms can be helpful (e.g. buccally, sublingually, rectally). However, please note that at high doses paradoxical agitation can be caused, and withdrawal symptoms can occur if weaned too quickly. In longer term use, benzodiazepines can lead to dependence and there is limited evidence of their effectiveness, so may not be the medication of choice in the long term.

Other medications with sedative effects can be helpful, particularly in generalised agitation (rather than anxiety itself), such as levomepromazine, which is used as an antiemetic at lower doses, but has sedative effects at higher doses. Chlorpromazine also works well through its sedating effects.

Antipsychotics, such as haloperidol also have an important role in treating confusion.

Whilst in adult populations, antidepressants (such as SSRI's) are used to treat anxiety disorders they are not commonly used for the initial treatment of paediatric anxiety (particularly in the palliative care setting). It would therefore be worth seeking psychology support for generalised anxiety states in contexts other than terminal stages that have not responded to non-pharmacological methods.

## Depression

If non-pharmacological treatment has not been effective, then SSRIs (Selective Serotonin Reuptake Inhibitors) are considered to be the safest class of antidepressant. Fluoxetine has the most evidence of efficacy.

Treatment has the disadvantage of taking two to three weeks to work. Risks and side effects must be presented to the child and families (limited evidence, increased risk of suicide etc).

Remember that with SSRIs there may be an increase in anxiety for the first two weeks.

In view of controversy and lack of evidence around other forms of SSRIs (except for fluoxetine) it is probably best to avoid them unless there is no other option (or advised by clinical specialist).

Paroxetine, venlafaxine, tricyclic antidepressants, and St John's Wort should **not** be used for the treatment of depression in children and young people.

Note: all antidepressants can cause withdrawal symptoms if stopped abruptly.

## Professional support

Whilst not the focus of this chapter, we should also recognise that paediatric palliative medicine is a very emotional speciality, and that professionals may also need support. Part of the role of a palliative care specialist is to also help support other professionals. Likewise, we all must recognise the stressors within ourselves, and that we too may need support.

## Disordered sleep/ insomnia

[304-332]

Sleep disturbance is described as a deficit in quantity and quality of sleep which results in lack of continuous sleep. Sleep disturbance is an umbrella (or collective) term for several single sleep issues, classified by the International Classification of Sleep Disorders (ICSD-3), see figure one. Disrupted sleep results in increased activity of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, metabolic effects, alterations to circadian rhythms and proinflammatory responses<sup>1</sup>.

### **Figure 1: International Classification of Sleep Disorders (ICSD-3):**

- Insomnia
- Sleep-related breathing disorders e.g., obstructive sleep apnoea
- Central disorders of hypersomnolence
- Circadian-rhythm sleep-wake disorders
- Parasomnias
- Sleep-related movement disorders

In clinical practice, the most common sleep problems identified in children with life-limiting conditions include problems with falling and staying asleep, symptoms relating to the circadian sleep-wake rhythm and symptoms related to nocturnal respiration. In addition, the differing sleep disorders tend to occur cumulatively, adding to the complexity of addressing this symptom.

The prevalence of sleep disturbance in children and young people with life-limiting conditions is high, and increasingly so in those children with severe neurological impairment with a prevalence rate between 50-80%. This is reflected in the published literature with a propensity for publications examining the correlation between neurodevelopmental disorders and sleep disturbance.

The impact of sleep disturbance on children and their families is significant. It can be associated with day-time drowsiness, headaches, depression, and work-related problems and exacerbating co-existing symptoms. Studies have demonstrated the concomitant relationship between sleep disturbance and pain. It is therefore unsurprising that there is a negative relationship between sleep disturbance and quality of life.

### **Causes**

***It is important to recognise that insomnia can often be a result of uncontrolled physical and/or psychological symptoms.***

- Environmental - noise levels, lighting, disturbed nighttime routine from giving medication or conducting procedures.
- Distressing symptoms including pain, dyspnoea and dysautonomia.

- Psychiatric and psychological - fear, anxiety, depression, hallucinations, delirium.
- Underlying disease - altered sleep patterns often associated with several neurodegenerative conditions.
- Medication-induced e.g., corticosteroids, diuretics, bronchodilators, psychostimulants.
- Medication withdrawal e.g., benzodiazepines.

### **The association between severe neurological impairment and sleep disturbance (pathophysiology)**

There are various areas of the brain involved in the regulation of sleep, and consequently impairment, or insult to any of these areas will result in disruption of sleep-wake cycles. Children at significant risk of poor sleep include those with midline structural malformations of the brain (e.g., holoprosencephaly), those with severe cerebral maldevelopment (e.g., hydrocephaly) and children with severe visual impairment. Children with significant neurological impairment can also experience several other issues which may contribute to their disturbed sleep, including muscle spasms, movement disorders, gastroesophageal reflux, pain from any source and obstructive sleep apnoea.

### **Investigations**

Children with sleep disturbance should have a thorough work-up and professionals may wish to consider the following approach in the management of these children:

#### **Clinical history**

Key points include:

- BEARS acronym can help during initial screening of a child's disrupted sleep - bedtime resistance/sleep onset delay; excessive daytime sleepiness; awakenings at night; regularity, patterns, and duration of sleep; snoring and other symptoms.
- Screen for underlying low mood/anxiety.
- Explore the environmental history (identify sensory stimulants, sleeping patterns of parents and siblings).
- Drug history (investigate current medications and the timing of medication administration, identify use of any stimulants).
- Family history.
- Screen for primary sleep disorder e.g., OSA.
- Physical examination

#### **Sleep questionnaires/ sleep diaries**

- Sleep diaries recorded over 24 hours for at least two consecutive weeks can be helpful in evaluating sleep disruption in children.
- Helps to guide routine history taking and give an objective overview of the sleeping pattern.
- Useful for illustrating the day-to-day variability in sleep patterns that may not be covered during history taking.
- Examples of sleep questionnaires and sleep diaries which may be useful include:



- The Sleep Disturbance Scale for Children: a helpful 26 item parent questionnaire to screen for primary sleep disorders in children and teenagers.
- Sleep Council Sleep Diary ([sleepcouncil.org.uk](http://sleepcouncil.org.uk)) or Sleep Charity Children's Sleep Diary ([thesleepcharity.org.uk](http://thesleepcharity.org.uk)).

Investigations which may be considered in children presenting with evidence of sleep disordered breathing include:

- **Oximetry** - Identifies clusters of desaturation.
- **Capnography** - Investigates for possible hypoventilation.
- **Respiratory polygraphy** - Investigates for possible sleep disordered breathing.
- **Polysomnography** - Overnight sleep study which measures several parameters to ascertain sleep quality.
- **Actigraphy** - Non-invasive method of monitoring rest/wake cycles.

## Management

A thorough history of the child's sleeping pattern can help identify the cause of sleep disturbance which will subsequently influence the management. A sleep diary kept by the child/parents can help the physician to gain further insight into the child's sleeping pattern.

### Non-pharmacological

#### Sleep hygiene

- Avoidance of stimulants (e.g., caffeine).
- Ensure a comfortable quiet and dark sleep environment.
- Avoidance of co-sleeping.
- No screen time in the bedroom.
- A strict bedtime routine.
- White noise.
- Encourage self-soothing.
- Object of reference e.g., comforter.

#### Physical activity

- Where possible, physical activity can increase sleep quality.

### Behavioural interventions

#### Parent education

- Teach parents behavioural skills to help facilitate optimal sleep routines.
- Reduce behaviours that inhibit sleep.
- Enable sleep boundaries to be set

#### Cognitive behavioural therapy (CBT)

- Recognised as an effective treatment for insomnia in a variety of populations.

- Merges aspects of cognitive principles to challenge cognitions and ultimately alter the behaviours that contribute to the maintenance of sleep disruption.

### **Complementary therapies**

- Trial of aromatherapy oils (bergamot and lavender known to be helpful) or massage for both child and parents.

### **Review current medications**

- Consider current medications and timing of administration
- Discontinue if able, or alter timing if resulting in symptoms overnight e.g., NSAIDs. resulting in dyspepsia or steroids causing wakefulness.

### **Pharmacological**

Medication should only be used to manage insomnia as a last resort when non-pharmacological strategies have been tried and were unsuccessful.

#### **Melatonin**

- The primary hormone produced by the pineal gland that influences sleep patterns.
- Enhances sleepiness and therefore effective in reducing the time it takes for children to fall asleep.
- Evidence of use for disordered sleep in children with cerebral palsy, ADHD and autism.
- Children/parents should be asked to keep a sleep diary prior to, and during use, to monitor effectiveness.
- Commence on lowest dose and titrate as needed.
- There is some evidence to suggest that children with severe neurological impairment may require higher doses than conventionally used (10-15mg at night).
- Most effective when given at same time every night.
- No significant adverse side effects identified in long term use of standard doses; the long-term effect of high doses is unknown.

#### **Chloral hydrate**

- Hypnotic and sedative drug.
- May be considered where there is a delay in sleep onset.
- Exact mechanism of action unknown.
- Trichloroethanol (active metabolite which chloral is rapidly converted into in the liver) is thought to result in the non-specific CNS depression associated with chloral.
- Can result in respiratory depression so use cautiously in sleep disordered breathing.

#### **Lorazepam**

- Long-acting benzodiazepine.
- Duration of action 4-6 hours; ideally administered up to 1 hour prior to bedtime.
- Only for use in the short term; dependence and tolerance can be problematic.
- Be aware: can result in agitation for some individuals.

#### **Clonidine**

- Central alpha 2 adrenergic receptor antagonist.
- Onset of action within 1h, peak effect 2-4h.
- Acts on the autoreceptors of presynaptic noradrenergic neurons to decrease their release of noradrenaline.
- Frequently used in the management of poor sleep in children with neurodisability although limited evidence of efficacy.
- Tolerance can be troublesome.

### **Gabapentin**

- Binds strongly to the alpha-2-delta site on voltage gated calcium channels.
- Peak effect around 3h.
- A good option if pain appears to be disturbing sleep.
- May take 1-2 weeks for improvement in symptoms.
- Titrate dose as per APPM formulary.

### **Amitriptyline**

- Tricyclic antidepressant.
- Mechanism of action not clear: thought to block the membrane pump mechanism required for the re-uptake of transmitter amines such as noradrenaline and serotonin therefore increasing their concentration in the brain.
- Peak effect 4-8h after administration.
- Consider aiding with sleep if pain also an issue.

### **Alimemazine/ Promethazine**

- Antihistamine.
- Blocks histamine and has a direct effect relaxing the brain.
- Only for use in the short term: sedative effects often reduced after multiple days of use.

## **Sleep Resources**

There are several websites which provide useful resources for professionals and parents as listed below:

### **Sleep Scotland**

Provides sleep counsellor training and teen sleep education package

Parent/carer telephone support line

<http://www.sleepscotland.org>

### **The Children's Sleep Charity**

Parent/carer telephone support line available

School and parent education package

Sleep practitioner training available

CPD updates

<http://www.thechildrenssleepcharity.org.uk>

### **Cerebra**

Provides parent telephone support and parent sleep workshops

<http://www.cerebra.org.uk>

#### SCOPE

Parent workshops and support available

<http://www.scope.org.uk/support/services/sleep-solutions>

#### Applications

Applications are available for electronic devices to help facilitate sleep in children and young people as illustrated below:

##### **Calm**

Sleep and meditation app

Subscription

Relaxation techniques and mindfulness

For pre school children to young adults



##### **Headspace**

Relaxation techniques and mindfulness

Subscription



##### **Breath: Meditation & Sleep**

Sleep music playlists, nature sounds,  
guided meditations, hypnotherapy and sleep  
stories

Free to download



##### **Moshi**

Sleep and mindfulness audio only app for  
children

Subscription



## Skin

[333-335]

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.

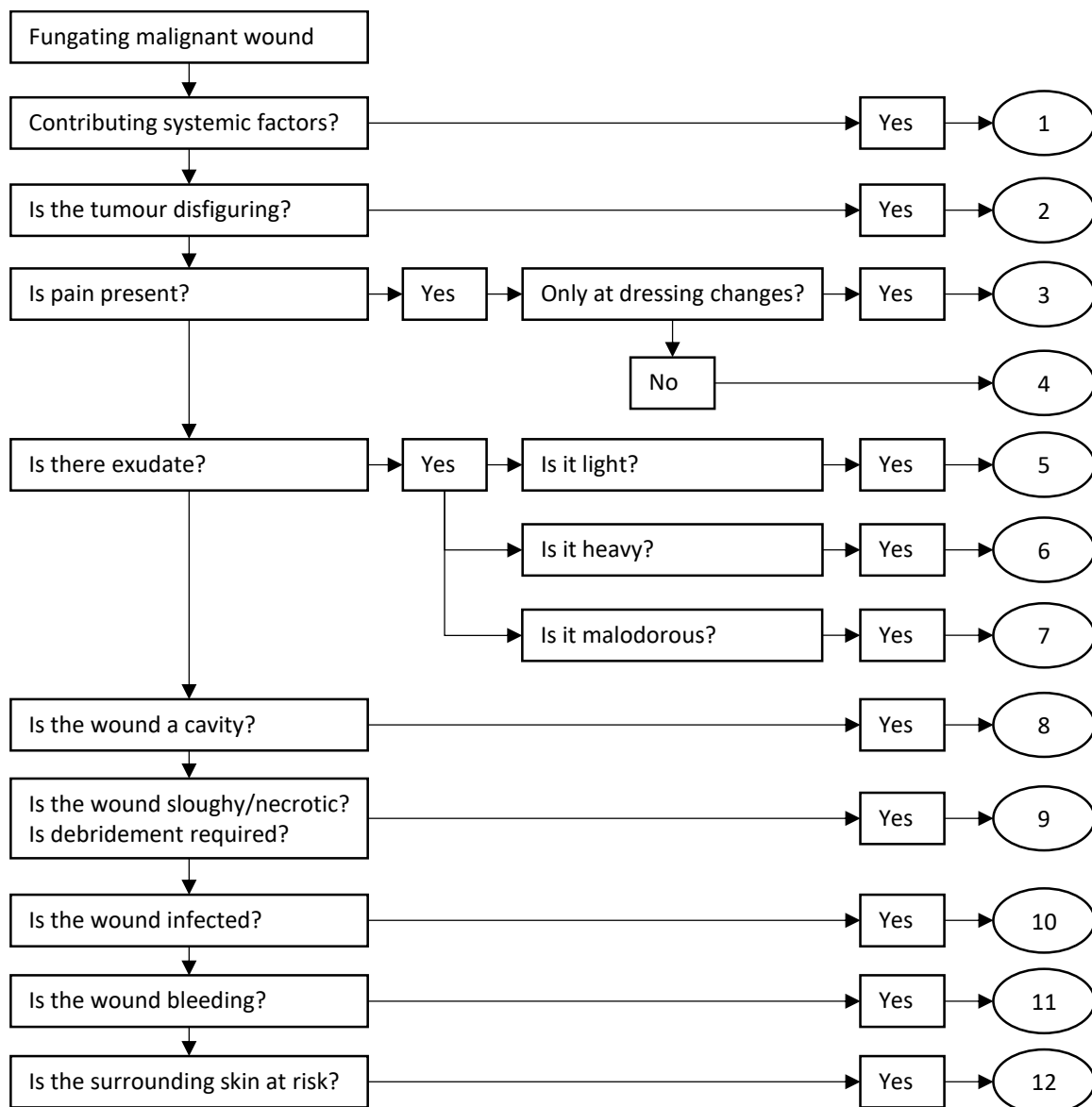
- Initial problems tend to start from pressure sores or friction burns.
- The skin at this stage can be protected with OpSite, Tegaderm or Cutifilm.
- Care must be taken when removing these dressings so as not to further damage the skin.
- Once it breaks down then DuoDerm or Spyrosorb can be used.
- 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.

**Table 1:** 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, Spyrosorb.	Occlusive but absorb exudates.	Facilitate autolysis of slough and eschar.
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	Lyof foam, 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 [336])

**Table 2:** 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.

# Tracheostomy care

## What is a tracheostomy?

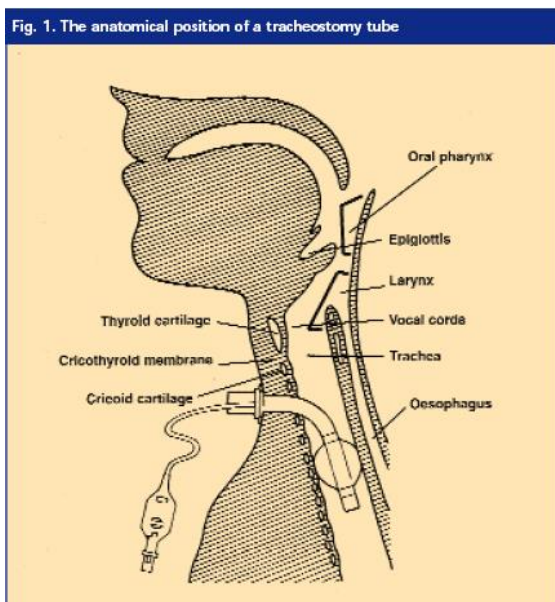
This is an artificial opening into the windpipe (trachea) which is held open by a tracheostomy tube. This helps the child to breathe easily; air now goes in and out through the tracheostomy, bypassing the mouth.

## Indications for a tracheostomy

A narrow upper airway.

The need for long term ventilation.

Bronchial toilet.



There are several types of tracheostomies. 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 always 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 the child is 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 always maintained.

## 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

- Child 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 of 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.

## Basic Symptom Control 2024

7. Look, listen and feel for breathing.
8. If not breathing, shout for help and 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  
4<sup>th</sup> Floor, Fry Building  
2 Marsham Street  
London  
SW1P 4DF

Tel: 020 7035 6330 (9-5 Monday to Friday).

Email: [DLCUCommsOfficer@homeoffice.gsi.gov.uk](mailto:DLCUCommsOfficer@homeoffice.gsi.gov.uk)

Web: <https://www.gov.uk/travelling-controlled-drugs>

## APPM Medicine Formulary.

We would like to thank Lynda Brook and the APPM for allowing us to share their most recent formulary. We have put the formulary in unedited so as not to disturb the drug dose layout. Hence the different font. All the original references for the formulary are available on <https://www.appm.org.uk/formulary/>

## Introduction

Welcome to the sixth APPM Formulary. This latest edition represents a substantive revision from the previous version. The entire formulary has been reviewed and updated incorporating recent published literature, specialist advice and feedback from formulary users. Many of the monographs have been extensively rewritten and references have been brought up to date. The formulary has also been completely reformatted, including greater use of tables and with the aim of improving clarity and navigability.

Notable changes are as follows:

- Substantially revised or reformatted opioid equivalence tables including new recommended approximate equi-analgesic ratios for morphine, diamorphine and oxycodone
- Use of a QR code to link the printed formulary directly to the APPM Website for updates and supplementary information
- Substantially revised or reformatted monographs: Aprepitant, Diamorphine, Midazolam, Morphine, Octreotide, Pamidronate, Risperidone
- New monographs: Alimemazine, Famotidine, Propantheline, Prucalopride, Oxybutynin
- Archived monographs: Arthrotec, Codeine, Dihydrocodeine, Lomotil, Ranitidine (as unavailable)
- New appendices:
  - Prolonged QT syndrome
  - Opioid stewardship
  - Buccal administration of liquid preparations
  - Dosing in obesity
- The table outlining compatibility of two drugs in continuous intravenous or subcutaneous infusion has been archived. Professionals are instead advised to consult the appropriate specialist text to inform the safe practice of combining multiple drugs in a single infusion
- Referencing updated with older references archived and greater emphasis on systematic reviews where available. The full references archive will continue to be available online on the APPM website
- New additions to the formulary and significant revisions clearly marked

- More consistent referencing to drugs known to prolong the QT-interval in the individual monographs
- Consistent referencing to available patient information from Medicines for Children Leaflets

We hope that other neonatal and paediatric palliative medicine formularies in books or hospitals in the UK and worldwide will continue to be based on the APPM Formulary. As ever we welcome feedback, comments, suggestions, and recommendations from healthcare professionals in the UK and across the world. Please contact [Lynda.Brook@alderhey.nhs.uk](mailto:Lynda.Brook@alderhey.nhs.uk)

The Formulary, together with versions translated into other languages, is available to download from the Association for Paediatric Palliative Medicine website [www.appm.org.uk](http://www.appm.org.uk)

Lynda Brook and Anita Aindow, September 2023

## Using the formulary

Drugs are presented in alphabetical order by generic name focusing primarily on routes and indications generally used in children's palliative care in the United Kingdom. Drugs are included in the formulary only when there is sufficient evidence either in the form of published peer reviewed literature, or established professional consensus for their safety, efficacy, and cost effectiveness. In some circumstances drug doses higher than quoted in the formulary may be recommended by specialists familiar with their use.

Dosing recommendations apply to all stated indications unless otherwise specified. The term "by mouth" refers to administration via the enteral route. See notes section for available information on administration via intra-gastric or jejunal tubes.

Common and important side effects and drug interactions are listed, particularly those likely to influence therapeutic decision making in paediatric palliative care. Clinicians are advised to consult the BNF, BNFC and relevant summary of product characteristics for a definitive list of all known side effects and drug interactions.

The most recent references are included focusing primarily on systematic reviews where available and monographs where additional justification for recommendations is required. Further references, including those archived from previous editions of the formulary, can be accessed on the APPM website by scanning the QR code below.

### Patient information leaflets

Patient information leaflets are included where available. Please note however that patient information may focus on use of the drug for another indication not necessarily in paediatric palliative medicine. Professionals are advised to review the available information for appropriateness before recommending for a patient.

### Prolonged QT-interval

Alerts regarding QT prolongation are provided for all drugs known to prolong QT-interval when used for the indications and doses. Other drugs that may prolong QT-interval in certain circumstances are indicated only if relevant to paediatric palliative medicine.

### Relation to BNFC

Doses recommended are generally consistent with those in the British National Formulary (BNF) or British National Formulary for Children (BNFC). Dose recommendations that are different to those in the BNFC are marked together with rationale.

## Accuracy of information



Every attempt has been made to ensure information presented here is accurate and up to date as of September 2023. Any critical updates or corrections will be posted on the APPM Formulary webpage which can be accessed by scanning the QR code.

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 via the Association of Paediatric Palliative Medicine.

## Weight or age-based dosing

Over the last few years there has been a general move towards age-based rather than weight-based dosing for children: the rationale being improved patient safety by avoiding the need for drug dose calculations. However, paediatric palliative medicine patients are frequently atypical in terms of weight for age or body composition. In general weight-based dosing options should be used if possible and these have been provided where available. When no weight-based dosing options are given, and patients are extremely small for their chronological age, consider starting at doses corresponding to the age-band normally associated with the patient's weight. For dosing in obesity, see specific monographs and also Appendix 7.

## Abbreviations

5HT <sub>2</sub>	5 hydroxytryptamine (serotonin) type 2 receptor
5HT <sub>3</sub>	5 hydroxytryptamine (serotonin) type 3 receptor
APLS	Advanced Paediatric Life Support
ALT	Alanine transaminase
AST	Aspartate transaminase
CD	Controlled drug
CIVI	Continuous intravenous infusion
cLQTS	Congenital long Q-T syndrome
CNS	Central nervous system
COX	Cyclo-oxygenase
CSCI	Continuous subcutaneous infusion
CSF	Cerebrospinal fluid
GFR	Glomerular filtration rate
IM	Intramuscular
IV	Intravenous
kg	Kilograms
MAD	Mucosal atomiser device
mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Authority
ml	millilitres
NHS	National Health Service (UK)
NICU	Neonatal intensive care unit
NK	Neurokinin type 1 receptor

NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
PICU	Paediatric intensive care unit
PO	By mouth (per oral)
PRN	As required
SC	Subcutaneous
SL	Sublingual
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
TdP	Torsades de Pointes
UK	United Kingdom
WFI	Water for injection
WHO	World Health Organisation

## Acetazolamide

### Use:

- Epilepsy
- Raised Intracranial Pressure-to reduce CSF production in obstructive causes, as an alternative to steroids

### Dose and route:

#### Epilepsy

By mouth using immediate release formulations, or by slow intravenous injection:

- **Neonate:** Initially 2.5mg/kg 2-3 times daily, followed by 5-7mg/kg 2-3 times daily (maintenance dose)
- **Child 1 month-11 years:** initially 2.5mg/kg 2-3 times daily, followed by 5-7mg/kg 2-3 times daily, maximum total daily dose 750mg (maintenance dose)
- **12 years and over:** 250mg 2-4 times daily, maximum total daily dose 1g

#### Raised intracranial pressure

By mouth or slow intravenous injection:

- 8mg/kg 3 times daily, increased as necessary, maximum 100mg/kg total daily dose

### Notes:

- Carbonic anhydrase inhibitor.

#### *Licensing*

- Licensed for childhood and adult epilepsy. Not licensed for raised intracranial pressure in children.

#### *Therapeutics*

- May give symptomatic benefit in the case of CSF obstruction including from inoperable brain tumours.
- May provide GABA-A receptor mediated analgesia at the spinal level, due to carbonic anhydrase inhibition.

#### *Contraindications, cautions*

- Contraindicated in sulphonamide sensitivity, adrenocortical insufficiency, hypokalaemia, hyponatraemia

#### *Side effects*

- Association with acute kidney injury (AKI) in critically ill children admitted to intensive care units

- May cause electrolyte disturbance with prolonged use (can be corrected with potassium bicarbonate), gastrointestinal disturbance, paraesthesia at higher doses and haematological abnormalities.
- Monitor blood count and electrolytes in prolonged use.

*Interactions*

- Potential for severe interactions with aspirin, lithium, valproate and zonisamide

*Administration*

- Tablets are scored and can be halved or quartered.
- Dissolving tablet in water produces a coarse dispersion that settles rapidly. For administration via feeding tubes, dissolve the required dose in 10ml water and rinse container to ensure the full dose is given.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Injection can theoretically be used via feeding tubes.
- Modified release capsule is not suitable for enteral tube administration.
- Alkaline pH: NOT appropriate for IM or SC administration

*Available as*

- Tablets 250mg, modified release capsules 250mg; 500mg injection (sodium salt, powder for reconstitution) Diamox®.



## Adrenaline (also known as Epinephrine)

### Use:

- Small external bleeds
- Upper airway obstruction (inflammatory/oedema cause)

### Dose and route:

#### Localised bleeding:

By topical application

- Soak gauze in 1:1000 (1mg/ml) solution and apply directly to bleeding point for up to 10 minutes

#### Upper airway obstruction:

By inhalation of nebulised solution:

- **Child 1 month-11 years:** 0.15-0.4ml/kg of 1:1000 (1mg/ml) solution, maximum 5ml per dose, diluted to 5ml with sodium chloride 0.9%. Repeat after 30 minutes if necessary
- **12 years and over:** 1-5ml of 1:1000 (1mg/ml) solution diluted to 5ml with sodium chloride 0.9%. Repeat after 30 minutes if necessary

## Notes

### *Licensing*

- Not licensed for upper airway obstruction, croup or localised bleeding

### *Side effects*

- Short term use only. Risk of ischaemic necrosis and rebound vasodilation with prolonged use.

### *Pharmacokinetics*

- Nebulised: duration of action 2-3 hours

### *Available as*

- Ampoules solution for injection 10mg/10ml, 5mg/5ml, 1mg/1ml and 500micrograms/0.5ml

## Alfentanil

### Use:

- Short acting synthetic lipophilic opioid analgesic derivative of fentanyl
- Alternative opioid in patients with end stage (4 or 5) renal failure, opioid related neurotoxicity or intolerance to other opioids
- Useful for breakthrough pain and procedure-related pain
- Used as analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia)

#### Important safety information

##### For all opioids

##### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose

### Dose and route:

#### Pain in patients already receiving regular strong opioids

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of opioid administered over the previous 24 hours

Convert to the equivalent dose of alfentanil using the table below (see also Appendix 1)

- Consider reducing the dose of alfentanil by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Alfentanil CSCI or CIVI	30:1	Divide 24hour morphine dose by 30	Morphine oral 60mg/24hours ÷ 30 = alfentanil CSCI 2mg/24hours
Morphine CSCI or CIVI	Alfentanil CSCI or CIVI	15:1	Divide 24hour morphine dose by 15	Morphine CSCI 30mg/24hours ÷ 15 = alfentanil CSCI 2mg/24hours

### Breakthrough pain in patients already receiving opioids

By subcutaneous, buccal and intranasal routes

- 1/10 to 1/6 (10%-16%) of the total CSCI dose as required, up to hourly

There is no direct correlation between the effective PRN-dose and the regular background dose: start with low dose and titrate according to response

### Procedure-related pain **SEEK SPECIALIST ADVICE**

By subcutaneous, buccal and intranasal routes

Administer at least 5 minutes before procedure, repeating if needed.

- **Child 2-11 years:** 5micrograms/kg single dose, maximum 250micrograms/dose
- **12 years and over:** 250-500micrograms single dose over 30 seconds. Subsequent doses 250micrograms

### Notes:

#### *Licensing*

- Licensed for perioperative use in children. Not licensed for pain relief in palliative care. Not licensed for buccal, sublingual, or intranasal administration. Not licensed for incident or breakthrough pain.

#### *Therapeutics*

- Rapid onset of action (less than 5 minutes after subcutaneous bolus injection), and short duration of action (less than 60 minutes). Even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Review dose and frequency of administration regularly.
- Useful for incident and breakthrough pain as faster onset, shorter acting and smaller volumes required compared with fentanyl. Not appropriate for titration of opioid requirements against the patient's pain due to short duration of action. No direct correlation between the effective PRN dose and the regular background dose.

- Limited information or evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.
- Useful in patients with severe renal failure (no dose reduction is needed). Avoid or reduce doses by 30-50% in severe hepatic impairment.
- Calculate starting doses in obese children based on ideal body-weight for height rather than actual body-weight.
- Potential alternative to diamorphine or fentanyl when higher doses of opiate are required but subcutaneous administration is difficult due to large volume of infusion.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

*Contraindications, cautions*

- Contraindicated in patients receiving MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Greater risk of addiction, tolerance and drug seeking behaviour particularly when administered via buccal or intranasal routes, compared with longer acting opioids.

*Side effects*

- Usual opioid side effects, hypothermia and muscle rigidity (which can be managed with neuromuscular blocking drugs).

*Pharmacokinetics*

- Half-life prolonged in neonates: risk of accumulation. Clearance may be increased in patients from 1 month to 12 years of age: higher doses may be needed.

*Interactions*

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by CYP3A4 inhibitors including aprepitant, ciprofloxacin, clarithromycin, erythromycin and fluconazole. Levels reduced by CYP3A4 inducers including carbamazepine and phenobarbital. Levels potentially increased by midazolam.

*Administration*

- Compatible with sodium chloride 0.9% or dextrose 5% as a diluent. Physically compatible with most drugs used in a syringe driver. Possible concentration-dependent incompatibility with cyclizine: use water for injection as diluent and observe for crystallisation.

*Available as*

- Injection (500 micrograms/ml in 2ml, 10ml and 50ml ampoules); Intensive care injection (5mg/ml in 1ml ampoule to be diluted before use). Nasal spray with attachment for buccal / SL use (5mg/5ml bottle available as special order from Torbay Hospital Manufacturing Unit Tel: 01803 664707, [torbaypharmaceuticals@nhs.net](mailto:torbaypharmaceuticals@nhs.net). Each 'spray' delivers 0.14ml = 140micrograms alfentanil. More costly than using injection preparation).

*CD*

- Schedule 2 CD

## Alimemazine (Trimeprazine) tartrate (NEW)

### Use:

- Urticaria
- Pruritus
- Anti-emetic
- Procedural sedation
- Short term treatment of sleep disturbance in children with suspected or definite neurodevelopmental disorder where other behavioural and pharmacological measures have failed

### Dose and route:

Doses as alimemazine *tartrate* (see notes below for other formulations)

#### Urticaria, pruritus, anti-emetic

By mouth

- **Child 6 months-1 year (specialist use only):** 250micrograms/kg, maximum 2.5mg/dose, 3–4 times daily
- **Child 2-4 years:** 2.5mg, 3–4 times daily
- **Child 5-11 years:** 5mg 3–4 times daily
- **12 years and over:** 10mg 2–3 times daily

#### Procedural sedation, night sedation

By mouth

1-2 hours before procedure or 1-2 hours before bed-time

- **Child 1 month-1 year (specialist use only):** 1-2mg/kg as a single dose
- **2 -11 years:** 1-2mg/kg not to exceed 60mg as a single dose
- **12 years and over:** Up to 30-60mg as a single dose

### Notes:

Sedative phenothiazine antihistamine

#### Licensing

- Unlicensed for treatment of urticaria or pruritus in children from the age of 6 months to 2 years. Licensed for sedation in children from 2-6 years. Licensed indications may differ between formulations

### *Therapeutics*

- Total daily doses of up to 100mg have been reported in adults

### *Contraindications, cautions*

- Contraindicated in neonates and children under 2 years except on specialist advice, epilepsy.
- Caution in patients with cardiac disease and those with, or at risk of prolonged QT, hypotension or risk of hypotension; may lower seizure threshold; pyloroduodenal obstruction; urinary retention; hepatic impairment and/or jaundice

### *Side effects*

- Respiratory depression, particularly at higher sedative doses, cardiac arrhythmia, mood and sleep disturbance, seizures, dystonia, photosensitivity especially at higher doses, neuroleptic malignant syndrome

### *Hepatic impairment, renal impairment*

- Contraindicated in severe renal failure and severe hepatic failure

### *Interactions*

- Sedative effects intensified when co-administered with other sedatives
- Increased antimuscarinic and sedative effects with anticholinergics including tricyclics, antihistamines and MAOIs
- Hypotensive effects intensified when co-administered with other hypotensive agents especially alpha adrenoreceptor blockers
- May reduce or abolish effects of clonidine

### *Administration*

- Dilute oral solution or oral syrup with an equal volume of water before administration via feeding tube. Tablets can be crushed and mixed with water for administration. The blue film-coating can be washed off the tablets to make them easier to crush. Without crushing they disperse in one to two minutes. Flush tube well before and after administration
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy

### *Available as*

- Oral syrup / liquid containing alimemazine tartrate 7.5mg/5ml, 10mg/5ml and 30mg/5ml; alimemazine tartrate 10mg tablets
- A variety of brands/generics available, and the syrup formulations contain high amounts of sucrose and ethanol. Check carefully. Oral solutions may be preferable to syrups in terms of sucrose and ethanol content. Liquid formulations may also contain methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed) and/or sodium sulfite anhydrous (E221) and sodium metabisulfite (E223), which may rarely cause severe hypersensitivity reactions and bronchospasm. Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25mg is equivalent to about 20mg of alimemazine

## Amitriptyline

### Use:

- Neuropathic pain
- Drooling, sweating, refractory cough
- Neuropathic pruritus

### Dose and route:

By mouth:

- **Child 2-11 years:** Initial dose of 200micrograms/kg (maximum 10mg) at night increased gradually, if necessary. Recommended maximum 1mg/kg/dose twice daily (under specialist supervision)
- **12 years and over:** Initial dose of 10mg at night increased gradually, if necessary, every 3-5 days to a suggested initial maximum of 75mg once daily

Higher doses up to 150mg daily in divided doses may be used in adults under specialist advice.

Twice daily dosing rarely needed. If necessary give 25-30% of daily dose in morning and 70-75% at night

### Notes:

#### *Licensing*

- Not licensed for use in children with neuropathic pain or pruritus, drooling, sweating or cough.

#### *Therapeutics*

- Evidence of benefit for neuropathic pruritus in adults.
- Analgesic effect unlikely to be evident for several days. Improved sleep and appetite are likely to precede analgesic effect.
- Benefit generally increases with higher doses; however benefit is lost at higher doses in some patients.
- Benefit in cough probably relates to reduction in cough reflex hypersensitivity.

#### *Contraindications, cautions*

- Contraindicated in severe liver impairment.
- Contraindicated in patients receiving MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Caution in mild/moderate hepatic impairment, heart block and arrhythmias.
- Caution in epilepsy: may lower seizure threshold

#### *Side effects*

- Main side effects limiting use in children include: constipation, dry mouth, blurred vision and drowsiness.

*Pharmacokinetics*

- Absorbed slowly from gastrointestinal tract. Peak plasma concentration occurs 4-8 hours after oral administration.

*Interactions*

- Metabolised by cytochrome P450 enzymes CYP2D6 and CYP2C19. Levels increased by drugs that inhibit CYP2D6 enzymes including fluoxetine and fluconazole, particularly in those who are poor CYP2D6 metabolisers. Levels reduced by drugs that induce CYP2D6 enzymes including carbamazepine, phenobarbital and phenytoin.
- Carbamazepine reduces plasma amitriptyline by up to 60%.
- Amitriptyline increases the effects of adrenaline/epinephrine. Manufacturer advises avoid.
- May reduce effect of clonidine

*Administration*

- Oral solution may be administered via an enteral feeding tube (mix with equal volume of water; no data for some of the preparations). No specific data available for administration of tablets via enteral feeding tube.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children leaflet "Amitriptyline for neuropathic pain":  
<https://www.medicinesforchildren.org.uk/medicines/amitriptyline-for-neuropathic-pain/>

*Available as*

- Tablets (10mg, 25mg, 50mg) and oral solution (10mg/5ml, 25mg/5ml, 50mg/5ml; other strengths may be available as 'specials').



## Aprepitant

### Use:

- Prevention and treatment of nausea and vomiting associated with moderate or highly emetogenic cancer chemotherapy in combination with a corticosteroid (usually dexamethasone) and a 5-HT<sub>3</sub> antagonist such as ondansetron
- Management of pruritus refractory to other treatment including paraneoplastic pruritus and drug related pruritus
- Cyclical vomiting
- Vomiting in gastrointestinal dystonia

### Dose and route:

#### Chemotherapy induced nausea and vomiting

By mouth:

Day 1: 1 hour before chemotherapy

- **Child 6 months-11 years** (and not less than 6kg): 3mg/kg (maximum 125mg) as a single dose
- **12 years and over:** 125mg as a single dose

Days 2 & 3: 1 hour before chemotherapy or in the morning if no chemotherapy is given

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) as a single dose
- **12 years and over:** 80mg as a single dose

#### Cyclical vomiting (NEW)

By mouth:

Prodromal phase, at least 30 minutes before emetic phase

**Child 6 months-11 years** (and not less than 6kg): 3mg/kg (maximum 125mg) as a single dose

- **12 years and over:** 125mg as a single dose

Days 2 & 3

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) as a single dose
- **12 years and over:** 80mg as a single dose

Prophylaxis

**Child 6 months-11 years** (and not less than 6kg): 3mg/kg (maximum 125mg) twice weekly

- **12 years and over:** 125mg twice weekly

### **Vomiting in gastrointestinal dystonia refractory to other anti-emetics (NEW)**

By mouth:

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) once daily
- **12 years and over:** 80mg once daily

### **Pruritus (NEW)**

By mouth:

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) once daily for 3-13 days. Then stop. If symptoms return, repeat course or reduce to alternate days.
- **12 years and over:** 80mg once daily for 3-13 days. Then stop. If symptoms return, repeat course or reduce to alternate days.

### **Notes:**

- Selective high-affinity antagonist at neurokinin-1 (NK-1) receptors in vomiting centre and chemoreceptor trigger zone.

#### *Licensing*

- 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 (>6kg).

#### *Therapeutics*

- Powerful anti-emetic but may be significantly less effective in reducing nausea

#### *Interactions*

- Aprepitant is a substrate, a moderate inhibitor and an inducer of cytochrome P450 enzyme CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with aprepitant CYP3A4 is inhibited. At the end of treatment aprepitant causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation
- Aprepitant therefore has the potential to interact with other drugs that are metabolised by these enzymes including alfentanil, buprenorphine, carbamazepine, dexamethasone, diazepam, diclofenac, domperidone, erythromycin, fentanyl, ibuprofen, midazolam and phenobarbital. *This list is not exhaustive-see advice.*

#### *Side effects*

- Common: include hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache and dizziness.

#### *Available as*

- Capsules 80mg and 125mg and powder for an oral suspension (125mg powder yielding on reconstitution an oral suspension 25mg/ml).

## Arachis Oil Enema

### Use:

- Faecal softener
- Faecal impaction

### Dose and route:

By rectal administration

- **Child 3-6 years:** 45-65ml as required (approximately 1/3 to 1/2 enema)
- **Child 7-11 years:** 65-100ml as required (approximately 1/2 to 3/4 enema)
- **12 years and over:** 100-130ml as required (approximately 3/4 to 1 enema).

### Notes:

#### *Licensing*

- Licensed for use in children.

#### *Therapeutics*

- Generally used as a retention enema to soften hard, impacted faeces. May be instilled and left overnight to soften the stool. Can be followed by use of a stimulant suppository or osmotic enema the following morning.

#### *Contraindications, cautions*

- Derived from peanuts, do not use in children with a known allergy to peanuts.
- Caution in inflammatory bowel disease and bowel obstruction.

#### *Administration*

- Warm enema in a water bath before use.
- Administration may cause local irritation.

#### *Available as*

- Enema, arachis (peanut) oil in 130ml single dose disposable packs.

## Atropine

### Use:

- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation

### Dose and route:

By sublingual route:

- **Neonate:** 20-40micrograms/kg/dose 2-3 times daily as required
- **Infant body-weight less than 10Kg:** 20-40micrograms/kg/dose 2–3 times daily as required
- **Child body-weight 10-19kg:** 250micrograms/dose 2–3 times daily as required
- **Child body-weight 20kg and over:** 250-500micrograms/dose, 2–3 times daily as required
- **12 years and over:** 500micrograms–1mg/dose 3-4 times daily as required

Use solution for injection 400 micrograms/ml, 600 micrograms /ml or 1mg/ml for administration of doses up to 250micrograms

Use 1% atropine eye drops (atropine 10mg/ml) for doses of 500micrograms and over. 1 drop of 1% atropine contains approximately 500micrograms of atropine

### Notes:

#### *Licensing*

- Not licensed for this indication or route of administration.

#### *Therapeutics*

- Research evidence based on 0.5% eye drops, only available outside the UK.
- Use only where symptom is affecting quality of life. Used 3rd line if glycopyrronium bromide or hyoscine hydrobromide are either unavailable or ineffective.
- Monitor for anticholinergic side effects: concurrent treatment with 2 or more antimuscarinic drugs increases risk of side effects, central toxicity and worsening quality of life. Children are particularly susceptible.

#### *Pharmacokinetics*

- Bioavailability of sublingual atropine is approximately 60%

#### *Side effects*

- May result in central nervous system stimulation.

#### *Available as*

- Available in UK as 1% (10mg/ml) eye drops (10 ml or 0.5ml pack size). Outside the UK 0.5% eye drops are also available. Solution for injection 400 micrograms/ml, 600 micrograms /ml, 1mg/ml ampoules. Pre-filled syringes: 500micrograms/5ml, 1mg/5ml and 3mg/10ml.

## Baclofen

### Use:

- Chronic severe spasticity and skeletal muscle spasm
- Dystonia
- Considered as third line for neuropathic pain
- Intractable hiccups

### Dose and route:

By mouth:

Initial dose

- **Child 1 month and over:** 300micrograms/kg/day in 3-4 divided doses, Increased gradually every 3-7 days to a usual maintenance dose of
  - 750micrograms-2mg/kg/day in divided doses

Maximum daily doses:

- **Child 1 month-7 years:** 40mg/day in divided doses
- **8 years and over:** 60mg/day in divided doses

By intrathecal injection:

- **Specialist teams only.** Maintenance 25-200micrograms daily via intrathecal pump.

### Notes:

#### *Licensing*

- Oral preparations licensed for treatment of spasticity and skeletal muscle spasm for all ages. Intrathecal injection licensed from 4 years of age.

#### *Therapeutics*

- Review treatment for spasticity if no benefit within 6 weeks of achieving maximum dose and withdraw over at least 1-2 weeks, more gradually if symptoms occur, if ineffective.
- Less likely to result in dependence or tolerance than diazepam.
- Doses starting at approximately 50% of those for spasticity have been used in severe intractable hiccups. May have direct effect on diaphragm.
- Impact of undesirable hypotonia may be minimised by reducing daytime and increasing evening doses.
- Intrathecal use by specialist only, for severe chronic spasticity that cannot be effectively managed by enteral treatment.

- Intrathecal injection can be administered as a short term CSCI to avoid sudden withdrawal when enteral and/or intrathecal routes are unavailable.
- Abrupt withdrawal, including through loss of the enteral route, intrathecal or pump failure can precipitate life threatening withdrawal syndrome with hyperactivity, increased spasticity, autonomic dysfunction and serious psychiatric reactions.
- Limited clinical data on the use of baclofen in children under the age of one year.

*Side effects*

- Common: drowsiness, nausea, hypotonia. Potential effects on swallow, airway protection, posture and function. Exacerbation of epilepsy. Increased gastric acid secretion.

*Contraindications, cautions*

- Contraindicated in active peptic ulcer disease.

*Hepatic impairment, renal impairment*

- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.

*Pharmacokinetics*

- Oral bioavailability >90%, onset of action hiccup 4-8hours, muscle spasm 1-2 days, spasticity 3-4 days

*Administration*

- Administer after food to reduce risk of gastric irritation.
- May be administered via enteral feeding tubes including gastrostomy or jejunostomy. (Specific data only available for some makes of liquid and tablet). 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. (Teva brand tablets produce a fine dispersion in 10 ml water).

*Patient information*

- See Medicines for Children leaflet "Baclofen for muscle spasm":  
<https://www.medicinesforchildren.org.uk/medicines/baclofen-for-muscle-spasm/>

*Available as*

- Tablets (10mg) and oral solution (5mg/5ml, 10mg/5ml). Solution for injection 50mg/ml. Intrathecal solution for infusion 500 micrograms/ml and 2mg/ml.

## Bethanechol

### Use:

- Urinary retention including opioid-induced urinary retention

### Dose and route:

By mouth:

- **Child 1-11 years:** 600micrograms/kg/day in 3 or 4 divided doses. Increasing if necessary and tolerated to a maximum of 1.2mg/kg/day in 3 or 4 divided doses. Maximum 10mg/dose.
- **12 years and over:** 10-25mg per dose 3 to 4 times daily. Increasing if necessary and tolerated to maximum of 50mg/dose

### Notes:

- Stimulates the parasympathetic nervous system, increasing bladder muscle tone and causing contractions which initiate urination.

#### *Licensing*

- Not licensed for use in children.

#### *Contraindications, cautions*

- Contraindicated in hyperthyroidism, peptic ulcer disease, asthma, cardiac disease and epilepsy.
- Safety and efficacy not established in children.

#### *Interactions*

- Effects antagonised by antimuscarinic agents

#### *Pharmacokinetics*

- Poorly absorbed by gastrointestinal tract. Therapeutic effect seen within 1 hour of oral administration.

#### *Administration*

- Administer 1 hour before or 2 hours after food to reduce likelihood of nausea and vomiting.
- Tablets may be crushed and dispersed in water for immediate administration via an enteral feeding tube; formulation for extemporaneous oral suspension is available.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

#### *Available as*

- 10mg and 25mg tablets licensed in UK, other strengths via importation companies and NOT licensed in UK.

## Bisacodyl

### Use:

- Constipation

### Dose and route:

By mouth:

- **Child 4 years and over:** 5-10mg once daily (recommended to be taken at night), adjust according to response. Increased as necessary up to 20mg daily

By rectum (suppository):

- **Child 2 years and over:** 5-10mg once daily; adjust according to response

### Notes:

- Stimulant laxative.

#### *Therapeutics*

- Acts by local effect on the colonic mucosa.
- Limited data exist on the safety and efficacy of regular and long term use. Prolonged or excessive use can cause electrolyte disturbance.

#### *Pharmacokinetics*

- Onset of action: tablets 10–12 hours, suppositories act in 20–60 min

#### *Administration*

- Suppositories must be in direct contact with mucosal wall.
- Enteric coated tablets. Do not crush.
- Not suitable for enteral tube administration.

#### *Available as*

- Gastro-resistant tablets (5mg) and suppositories (5mg, 10mg).



## Buprenorphine

### Use:

- Moderate to severe pain
- Alternative opioid in patients with end stage (4 or 5) renal failure

#### Important safety information

##### For all opioids

##### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose

### Dose and route:

#### **Stable pain in patients already receiving regular strong opioids**

By transdermal patch:

- By titration or convert using oral morphine equivalent (OME) see Appendix 1. Not suitable for dose titration in patients with unstable pain.
- Consider reducing the dose of buprenorphine by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Buprenorphine patches are *approximately* equivalent to the following 24-hour doses of oral morphine

#### **7 day patches**

Oral morphine 12mg/24hours	≡	Buprenorphine 5micrograms/hour
Oral morphine 24mg/24hours	≡	Buprenorphine 10micrograms/hour
Oral morphine 36mg/24hours	≡	Buprenorphine 15micrograms/hour
Oral morphine 48mg/24hours	≡	Buprenorphine 20micrograms/hour

#### **3 or 4 day patches**

Oral morphine 84mg/24hours	≡	Buprenorphine 35micrograms/hour
Oral morphine 126mg/24hours	≡	Buprenorphine 52.5micrograms/hour
Oral morphine 168mg/24hours	≡	Buprenorphine 70micrograms/hour

Systemic analgesic concentrations are generally reached within 12–24 hours after applying patch, but levels continue to rise for 32–54 hours (pharmacokinetic profile may differ slightly between preparations, check SPC for full details).

If converting from:

- 4-hourly oral morphine: administer regular morphine doses for the first 12 hours after applying the patch.
- 12-hourly slow release morphine: apply the patch and administer 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 morphine infusion: continue the infusion for 8- 12 hours after applying the patch.

### **Pain in opioid naive patients**

By sublingual route

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child body-weight less than 25kg:** 5micrograms/kg/dose, maximum 100micrograms/dose, every 8 hours (using injection solution)
- **Child body-weight 25–37.5 kg:** 100micrograms every 6-8 hours
- **12 years and over body-weight 40kg and over:** 200micrograms every 6-8 hours

Titrate the dose every 4–5 days, based on analgesic requirements. Typical adult dose 800micrograms–1.2mg/24hours, given as 200–400micrograms every 6-8 hours

By subcutaneous, intramuscular or slow intravenous injection

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child 6 months-11 years:** 3micrograms/kg/dose, maximum 300micrograms, every 6–8 hours.
- **12 years and above:** 300 micrograms every 6–8 hours.

Titrate the dose, based on analgesic requirements up to a typical adult maximum dose of 600mg every 6-8 hours.

### Notes:

- Strong opioid with both agonist and antagonist properties.

#### *Licensing*

- Sublingual tablets not licensed for use in children < 6 years old. Patches not licensed for use in children.

#### *Therapeutics*

- Doses quoted for opioid naive patients reflect the lower end of ranges quoted by manufacturers and BNFC in view of equianalgesic ratios and clinical experience in both adult and paediatric palliative care.
- Ceiling effect for respiratory depression, however life- threatening respiratory depression can still occur.
- Causes less constipation than some other opioids.
- May be particularly beneficial in neuropathic pain and hyperalgesia
- Sublingual administration not appropriate for breakthrough pain due to long duration of action
- Negligible bioavailability if swallowed due to extensive first pass metabolism
- Effects only partially reversed with naloxone at conventional doses. Theoretical risk of withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Has been given as continuous intravenous or subcutaneous infusion over 24 hours. Relatively long half-life means that equianalgesic studies based on single doses are likely to under-represent equianalgesia as a continuous infusion
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

#### *Caution*

- Caution in hepatic impairment.
- Rate of absorption from patch is affected by temperature with risk of accidental overdose including respiratory depression: caution with pyrexia or increased external temperature such as hot baths.
- Remove patches before MRI scanning due to risk of burns.

#### *Side effects*

- Patches may cause contact dermatitis. This may be reduced by topical application of budesonide inhaler spray to the area where the patch is to be applied.

#### *Pharmacokinetics*

- Clearance may be faster in some children.

- Duration of action in adults 6-8 hours versus 4-5 hours for morphine. Single-dose studies are therefore likely to underestimate the relative equianalgesic ratio of buprenorphine. Opioid potencies should be considered as an approximate guide, particularly for children for whom very little pharmacokinetic data is available. See Appendix 1 for approximate opioid equivalent data

#### *Interactions*

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit these enzymes including ciprofloxacin, erythromycin, and fluconazole. Levels reduced by drugs that induce these enzymes including carbamazepine and phenobarbital.

#### *Administration*

- MHRA advises that *fentanyl* matrix patches must not be cut due to the risk of life threatening and potentially fatal opioid toxicity. Similar considerations would be expected to apply to cutting buprenorphine patches. Buprenorphine patches should therefore not generally be cut. A decision to cut a buprenorphine matrix patch must be made on a case-by-case basis, weighing up the potential risks and benefits. Cut matrix (see Summary of Product Characteristics) patches diagonally if a smaller dose is required. Only matrix patches can be cut.
- For intravenous infusion dilute in sodium chloride 0.9% to a concentration of 15micrograms/ml. For subcutaneous infusion dilute in sodium chloride 0.9%. Limited compatibility data for mixing with other drugs used in palliative care

#### *Available as*

- *Tablets* (200micrograms, 400micrograms) for buccal administration. Tablets may be halved. Higher strength sublingual tablets also available but these are indicated as an adjunct in the treatment of opioid dependence. Take care with prescribing.
- *Patches*: several brands (and generics) of transdermal patches with 7 day, 4 day (96 hour) and 3 day (72 hour) release profiles. Patch size expressed in micrograms/hour. Only matrix patches can be cut. Prescribe by brand where possible: caution when switching between formulations.
- *7 day patches*: BuTrans®, Butec®, Bupramyl®, Panitaz®, Reletrans®, Sevodyne®. Available as 5micrograms /hour for 7 day), 10micrograms /hour for 7 days, 15micrograms/hour for 7 day) and 20micrograms/hour for 7 days
- *4 day (96 hour) patches*: Bupeaze®, Buplast®, Relevtec®, TransTec®. Available as 32.5micrograms/hour for 96 hours, 52.5micrograms/hour for 96 hours, and 70micrograms/hour for 96 hours
- *3 day (72 hour) patches*: Hapactasin®-applied every 72 hours. Available as 35micrograms/hour for 72 hours, 52.5micrograms/hour for 72 hours and 70micrograms/hour for 72 hours
- *Injection*: for intravenous or subcutaneous injection solution 300micrograms/ml

#### *CD*

- CD Schedule 3 (CD No Register). Local protocols may require safe storage.

## Carbamazepine

### Use:

- Neuropathic pain
- Hyperkinetic movement disorders
- Anticonvulsant

### Dose and route:

By mouth:

- **Neonates:** Experience is limited. Initial dose 5mg/kg twice daily
- **Child 1 month-11 years:** Initial dose of 5mg/kg at night or 2.5mg/kg twice daily, increased as necessary by 2.5-5mg/kg every 3–7 days; usual maintenance dose 5mg/kg 2–3 times daily.

Total daily doses of up to 20mg/kg/day in divided doses have been used

- **12 years and over:** Initial dose of 100–200mg 1–2 times daily; increased slowly to usual maintenance of 200-400mg 2–3 times daily.

Maximum total daily dose 1.8 g/day in divided doses

By rectum:

- **Child 1 month and over:** Use approximately 25% more than the oral dose, maximum single dose 250mg, up to 4 times daily.

### Notes:

#### *Licensing*

- Not licensed for use in children with neuropathic pain. Suppositories licensed for short term use only.

#### *Therapeutics*

- May cause hyperalgesia on abrupt withdrawal.
- Different preparations may vary in bioavailability: avoid changing formulations or brands.
- Suppositories of 125mg are approximately equivalent to 100mg tablets but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).
- Use ideal body weight (Appendix 7) when calculating doses in obese children

#### *Side effects*

- Can cause serious blood, hepatic, and skin disorders. Parents should be taught how to recognise signs of these conditions, particularly leucopenia.
- Associated with osteopenia and increased risk of fractures. Consider vitamin D supplementation with long term use.
- Neuroleptic malignant syndrome

*Interactions*

- Induce of cytochrome P450 enzymes CYP2C9 and CYP3A4. Reduces levels of drugs metabolised by these enzymes including alfentanil, amitriptyline, buprenorphine, clobazam, clonazepam, dexamethasone, diazepam, diclofenac, domperidone, erythromycin (erythromycin also increases carbamazepine levels), fentanyl, haloperidol, methadone, midazolam, paracetamol (with increased risk of liver toxicity), risperidone and tramadol. *This list is not exhaustive-see advice.*

*Administration*

- Oral liquid has been administered rectally-should be retained for at least 2 hours if possible but may have a laxative effect.
- Use the liquid preparation for administration via an enteral feeding tube. Dilute with equal volume of water to minimise adsorption to the feeding tube immediately prior to administration. There may be some tube resistance but not blockage when administering via enteral feeding tubes due to high viscosity of liquid.
- Doses above 800mg/day may cause bloating due to the sorbitol content of the liquid. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy. An increase in side effects such as dizziness is possible owing to the rapid delivery into the small bowel. Consider decreasing the dose and increasing the dosing frequency if side effects are problematic.

*Patient information*

- See Medicines for Children leaflet: "Carbamazepine (oral) for preventing seizures"  
<https://www.medicinesforchildren.org.uk/medicines/carbamazepine-oral-for-preventing-seizures/>

*Available as*

- Tablets (100mg, 200mg, 400mg), liquid (100mg/5 ml), suppositories (125mg, 250mg), and modified release tablets (200mg, 400mg).

## Celecoxib

### Use:

- Pain, inflammatory pain, bone pain, stiffness. Not used first line
- Post-operative pain where other non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated

### Dose and route:

By mouth:

- **Child over 2 years:**
  - Body-weight 10-25 kg:** 2-3mg/kg/dose twice daily, maximum 50mg twice daily
  - Body-weight more than 25 kg:** 100mg twice daily
- **Over 16 years:** 100mg twice daily, increased in severe pain to 200mg twice daily

### Notes:

- Selective cyclo-oxygenase-2 inhibitor.

#### *Licensing*

- Not licensed in the UK for use in children.

#### *Therapeutics*

- Dose based on management of juvenile rheumatoid arthritis.
- No difference in tolerability or efficacy has been shown between the selective cox-2 inhibitors (etoricoxib, celecoxib) and the non-selective NSAID, naproxen.
- Parecoxib may be an alternative if the enteral route is not available.
- Does not increase bleeding time.

#### *Contraindications, cautions*

- Caution in known CYP2C9 slow metabolizers.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

#### *Side effects*

- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term.
- 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. Consider prescription of a proton pump inhibitor with prolonged use. May exacerbate Crohn's disease.

#### *Hepatic impairment, renal impairment*

- Caution in renal impairment: avoid in severe renal impairment.
- Caution in hepatic impairment.

#### *Interactions*

- Inhibitor of cytochrome P450 enzyme CYP2D6. May increase the plasma concentrations of other drugs metabolized by this enzyme including amitriptyline, ondansetron and oxycodone.
- Metabolised by CYP2C9. Levels increased by drugs that inhibit this enzyme including fluconazole and in known CYP2C9 slow metabolisers. Levels reduced by drugs that induce this enzyme including carbamazepine
- Reduce dose of celecoxib by 50% if administered with fluconazole.

*Administration*

- 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.

*Available as*

- Capsules 100mg, 200mg. Also available in UK as an unlicensed 'special' oral suspension (100mg/5ml Quantum Pharmaceuticals)



## Chloral hydrate

### Use:

- Seizures in severe epileptic encephalopathy (seek specialist advice)
- Status dystonicus (seek specialist advice)
- Short term (up to 2 weeks) treatment of insomnia in children and young people with suspected or definite neurodevelopmental disorder where other behavioural and pharmacological measures have failed
- Procedural sedation in neonates

### Dose and route:

#### Seizures, status dystonicus, insomnia

##### By mouth or rectum:

- **Neonate, child 1 month-11 years:** Initial dose of 30mg/kg as a single dose at night. May be increased to 50mg/kg at night or when required up to 6-8 hourly.  
Maximum single dose 1g
- **12 years and over:** Initial dose of 500mg as a single dose at night or when required up to 6-8 hourly. Dose may be increased if necessary to 1-2 g.  
Maximum single dose 2g

#### Procedural sedation in neonatal intensive care

##### By mouth or rectum:

- **Neonate:** for sedation for procedures in NICU: 30–50mg/kg 45–60 minutes before procedure; doses up to 100mg/kg may be used with respiratory monitoring.

### Notes:

#### *Licensing*

- Not licensed for agitation, epilepsy or status dystonicus. Not licensed in infants under 2 years for insomnia. Use for treatment of severe insomnia in children and adolescents restricted by MHRA/CHM (2021) to those with a suspected or definite neurodevelopmental disorder when insomnia is interfering with daily life and other therapies have failed.

#### *Therapeutics*

- Use in insomnia only when insomnia is interfering with daily life. Long term use in insomnia only under specialist guidance
- Use in movement disorders or epileptic encephalopathy should be under the supervision of a named consultant with appropriate experience and competency in paediatric neurology, neurodisability or palliative care. The lowest effective dose should be used, at the lowest frequency and for the shortest period possible. The need for on-going use should be regularly reviewed.

- May cause agitation if withdrawn suddenly
- Enteral solution contains propylene glycol which may accumulate to potentially harmful levels with repeated dosing in neonates.

*Side effects*

- Allergic dermatitis; ataxia; confusion; delirium (more common on abrupt discontinuation); GI disorders
- Carcinogenic at high doses in rodents

*Pharmacokinetics*

- Accumulates with prolonged use
- Prolonged half-life in neonates.

*Hepatic impairment, renal impairment*

- Avoid in severe renal or hepatic impairment.

*Administration*

- By mouth: mix with plenty of juice, water, or milk to reduce gastric irritation and disguise the unpleasant taste. Light-sensitive so needs to be given as soon as it is drawn up.
- For rectal administration use oral solution or suppositories (available from 'specials' manufacturers).
- Chloral hydrate oral solution may be administered via enteral feeding tubes. Dilute with water before administration, ideally to 2 or 3 times the original volume as tolerated, to reduce risk of gastric irritation. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Tablets (chloral betaine 707mg = chloral hydrate 414mg— Welldorm®), oral solution (143.3mg/5ml, 500mg/5ml). Oral solutions contain propylene glycol. The RCPCH and NPPG recommend that, when a liquid formulation of chloral hydrate is required, 500 mg/5 mL is used.
- Suppositories (available as various strengths 25mg, 50mg, 60mg, 100mg, 200mg, 500mg from 'specials' manufacturers).

## Chlorpromazine

### Use:

- Hiccup
- Nausea and vomiting in end-of-life care (where other drugs are unsuitable)
- Agitated delirium in end-of-life care

### Dose and route:

By mouth:

- **Child 1-5 years:** 500micrograms/kg 6-8 hourly, adjusted according to response, maximum 40mg daily
- **Child 6-11 years:** 10mg 6-8 hourly, adjusted according to response, maximum 75mg daily.
- **12 years and over:** 25mg 6-8 hourly adjusted according to response, maximum 150mg daily

Total daily dose can also be given once daily at night

### Notes:

#### *Licensing*

- Not licensed in children for intractable hiccup.

#### *Therapeutics*

- Can be given rectally at doses of approximately twice those used via oral route

#### *Cautions*

- Caution in cardiovascular disease, neurological impairment including CNS depression, epilepsy, myasthenia gravis, severe respiratory disease, blood dyscrasias: monitor blood counts if unexplained infection or fever.

#### *Side effects*

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Photosensitisation may occur with higher dosages: avoid direct sunlight.
- Extrapyramidal side effects, neuroleptic malignant syndrome
- Risk of contact sensitisation: tablets should not be crushed; solution should be handled with care.

#### *Hepatic and renal impairment*

- Caution in hepatic impairment and jaundice: can precipitate coma.
- Caution in renal impairment: increased cerebral sensitivity. Start with small dose.

#### *Administration*

- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Tablets coated (25mg, 50mg, 100mg), oral solution (25mg/5ml, 100mg/5ml).  
Suppositories from specialist manufacturers

## Clobazam

**Clobazam** has been confused with **clonazepam**; care must be taken to ensure the correct drug is prescribed, dispensed and administered.

### Use:

- Adjunctive therapy for epilepsy
- Short term 'add on' therapy for epilepsy exacerbations related to hormonal changes or intercurrent illness

Important safety information

#### **For all benzodiazepines**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

By mouth:

- **Child 1 month-5 years:** Initial dose of 125micrograms/kg twice daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 250micrograms/kg twice daily. Maximum 500micrograms/kg, 15mg single dose, twice daily
- **Child 6 years and over:** Initial dose of 5mg daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 300micrograms/kg-1mg/kg daily. Maximum 60mg daily.

Daily doses of up to 30mg may be given as a single dose at bedtime, higher doses should be divided.

### Notes:

#### *Licensing*

- Not licensed for use in children less than 6 years of age. Not licensed as monotherapy.

*Therapeutics*

- Avoid abrupt withdrawal, except when being used for short courses. Caution when changing between different formulations.
- Tolerance in longer term use may be managed by 'switching/rotating' benzodiazepines.

*Side effects*

- Risk of increased somnolence or sedation when co-administered with cannabidiol, or opiates
- Side effects similar to other benzodiazepines: children are more susceptible to sedation and paradoxical emotional reactions.

*Pharmacokinetics, interactions*

- Pharmacokinetics influenced by age and co-administration of other medication. Dose adjustment may be needed when co-administered with strong or moderate CYP2C19 inhibitors.

*Administration*

- Tablets can be administered whole, or crushed and mixed in soft food. The 10mg tablets can be divided into equal halves of 5mg. Clobazam can be given with or without food. Tablets take 1 to 5 minutes to disperse in water. Both oral liquid and tablets dispersed in water may be administered via enteral feeding tubes.

*Patient information*

- See Medicines for Children leaflet "Clobazam for preventing seizures"  
<https://www.medicinesforchildren.org.uk/medicines/clobazam-for-preventing-seizures/>

*Available as*

- Tablets 10mg, Oral liquid (10mg/5ml, 5mg/5ml-care with differing strengths), capsules and oral suspension available from special manufactures
- Clobazam is not prescribable in NHS primary care except for the treatment of epilepsy; endorse prescription 'SLS'.

*CD*

- CD Schedule 4, part 1 (CD4-1).

## Clonazepam

Clonazepam has been confused with clobazam; care must be taken to ensure the correct drug is prescribed, dispensed and administered.

### Use:

- Tonic-clonic seizures
- Partial seizures
- Cluster seizures
- Myoclonus
- Neuropathic pain
- Restless legs
- Anxiety, including anxiety associated with dyspnoea, panic attacks
- Oral dysaesthesia in the adolescent

#### Important safety information

##### For all benzodiazepines

##### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The **APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose

### Dose and route:

#### Epilepsy

By mouth

- **Child 1 month-11 months:** Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 500micrograms–1mg at night, or in 2-3 divided doses.
- **Child 1-4 years:** Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 1–3mg at night, or in 2 -3 divided doses.
- **Child 5-11 years:** Initially 500micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6mg at night or in 2 -3 divided doses
- **12 years and over:** Initially 1mg at night for 4 nights, increased over 2–4 weeks to usual maintenance of 4–8mg at night, or in 2-3 divided doses.

Higher doses may be used in complex seizure disorders under guidance from a paediatric neurologist

### **Anxiolysis, neuropathic pain, myoclonus and restless legs**

By mouth

- **Child 1 month-11 months:** Initially 125micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 250–500micrograms at night, or in 2-3 divided doses.
- **Child 1-4 years:** Initially 125micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 500micrograms-1.5mg at night, or in 2 -3 divided doses.
- **Child 5-11 years:** Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 1.5–3mg at night or in 2 -3 divided doses
- **12 years and over:** Initially 500micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 2–4mg at night, or in 2-3 divided doses.

### **Oral dysaesthesia (burning mouth syndrome)**

- Rinse with 100micrograms/ml solution

### **Notes**

#### *Licensing*

- Licensed for use in children for status epilepticus and epilepsy. Not licensed for neuropathic pain. Tablets licensed in children. Not licensed in the UK for SC use.

#### *Therapeutics*

- Effective anticonvulsant often used as a 3<sup>rd</sup> line “add-on”.
- Avoid abrupt withdrawal, except when being used for short courses. Caution when changing between different formulations
- Tolerance in longer term use may be managed by ‘switching/rotating’ benzodiazepines.
- Dose may be increased for short periods of 3-5 days during times of increased seizures e.g. from viral illness.
- Approximately 20 times more potent than diazepam as an anxiolytic-sedative. (i.e. 250micrograms clonazepam equivalent to 5mg diazepam orally or 2.5mg IV/SC midazolam). See Appendix 4.
- Has been used as a subcutaneous or intravenous infusion in status epilepticus resistant to other anticonvulsants. However, the injection is no longer available in the UK. Intravenous or subcutaneous doses are approximately equal to oral doses. Due to the long half -life a loading dose should be given in patients not already receiving clonazepam
- Doses of up to 1.4mg/kg/24hours have been used in status epilepticus in PICU environment.

#### *Contraindications, cautions*

- Contraindicated in myasthenia gravis.



- Avoid in acute or severe respiratory failure unless imminently dying. Caution in chronic respiratory disease or sleep apnoea.
- Avoid abrupt withdrawal.

*Side effects*

- Associated with salivary hypersecretion and drooling.

*Pharmacokinetics*

- Oral bioavailability >80%; the same dose can be used when converting from PO to IV or SC routes.
- Long elimination half-life of up to 60 hours. Infusions may take up to 6 days to reach steady state. Risk of accumulation and toxicity. Consider loading dose to reach steady state more quickly.

*Hepatic and renal impairment*

- Caution in mild or moderate hepatic impairment: avoid in severe hepatic impairment.

*Patient information*

- See Medicines for Children leaflet: “Clonazepam for preventing seizures”  
<https://www.medicinesforchildren.org.uk/medicines/clonazepam-for-preventing-seizures/>

*Administration*

- Licensed oral liquid formulation contains alcohol. Tablets or other unlicensed non-alcohol-containing liquid preparations are therefore preferred.
- Tablets may be dispersed in water for oral administration or administration via a feeding tube.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Adheres to plastic tubing. Tablets should be dispersed in at least 30ml of water to prevent binding to enteral feeding tubes. Flush enteral feeding tubes well after administration. Use non-PVC tubing for infusions.
- Diluted clonazepam injection is stable for up to 12 hours. Infusions should ideally be changed every 12 rather than every 24 hours.
- Compatible with most drugs commonly administered via continuous subcutaneous infusion via syringe driver. Dilute with water for injection or sodium chloride 0.9%.

*Available as*

- Tablets (500micrograms scored, 1mg, 2mg scored); liquid (500micrograms in 5ml and 2mg in 5ml now available as licensed preparations from Rosemont, but neither are licensed for use in children due to high alcohol content; other unlicensed oral liquids are available from specials manufacturers); clonazepam drops 2.5mg/ml available from some special manufacturers; injection (1mg/ml unlicensed import).
- The RCPCH and NPPG recommend that, when a liquid special of clonazepam is required, the 2mg/5ml strength is used:

*CD*

- CD Schedule 4 part 1 (CD4-1).

## Clonidine

### Use:

- Anxiety / sedation (prior to procedure)
- Pain / sedation / opioid sparing / prevention of opioid withdrawal effects
- Regional nerve block
- Spasticity / dystonia
- Status dystonicus
- Hypertensive crisis in autonomic dysreflexia
- Behavioural symptoms of irritability, impulsiveness, aggression

### Doses and route:

#### Pain, sedation, opioid sparing, prevention of opioid withdrawal effects, spasticity, movement disorder

By mouth or intravenous bolus:

- **Child 1 month and over:** Initial dose 1micrograms/kg/dose 3-4 times daily. Increase gradually as needed and tolerated to maximum of 5micrograms/kg/dose four times daily.

For long term use consider conversion to a transdermal patch once an effective dose has been established

By transdermal patch

Conversion from oral, intravenous or subcutaneous routes

Clonidine 100-150micrograms/24hours	≡	Clonidine 2.5mg patch (delivers 100micrograms/24hours)
Clonidine 150-250micrograms/24hours	≡	Clonidine 5mg patch (delivers 200micrograms/24hours)
Clonidine 250-350micrograms/24hours	≡	Clonidine 7.5mg patch (delivers 300micrograms/24hours)

If more than 2.5mg patch to be used i.e.200micrograms/24hours, consider using 2 smaller patches to be changed on different days of the week to reduce end of dose effect.

Therapeutic clonidine levels are achieved 2 to 3 days after initial application of patch. Oral, intravenous or subcutaneous clonidine therefore needs to be reduced gradually after applying the patch:

Apply patch on day 1.

Day 1: continue 100% of oral/IV dose

Day 2: reduce to 50% of oral/IV dose

Day 3: reduce to 25% oral/IV dose

Day 4: patient will only need patch

By continuous intravenous or subcutaneous infusion (most experience on PICU)

- **Child over 1 month:** 0.1-2micrograms/kg/hour:  
approximately 2.5-50micrograms/kg/24hours

Usual starting doses:

- **Child less than 6 months:** 0.4micrograms/kg/hour  
approximately 10micrograms/kg/24hours
- **Child 6 months and over:** 0.6micrograms/kg/hour, approximately  
14micrograms/kg/24hours

Total daily dose can also be given as subcutaneous injection in two divided doses

### **Behavioural problems, tics, Tourette's syndrome:**

By mouth:

- **Child over 4 years:** Initial dose of 25micrograms at night. Increase as necessary after 1-2 weeks to 50micrograms at night. Dose can be further increased by 25micrograms every 2 weeks. Recommended maximum 5micrograms/kg/day or 300micrograms/day

For long term use consider conversion to a transdermal patch (see above) once an effective dose has been established

### **Anxiety, procedural sedation, autonomic dysreflexia:**

By mouth, or buccal/sublingual (using injection solution or oral tablets):

- **Neonate:** 4micrograms/kg as a single dose
- **Child 1 month and over:** 4micrograms/kg as a single dose, maximum 150 micrograms/ dose.

Premedication given 45-60 minutes before procedure

For autonomic dysreflexia a further dose up to 2micrograms/kg can be given after an hour if required

### **Regional nerve block (specialist use only):**

- **Child 3 months and over:** 1-2micrograms/kg clonidine in combination with a local anaesthetic.

## Notes:

- Mixed alpha-1 and alpha-2 agonist (mainly alpha-2). Appears to have synergistic analgesic effects with opioids and prevents opioid withdrawal symptoms. Also useful for its sedative effect. Use established in ADHD, behavioural problems and tics.

### *Licensing*

- Not licensed for use in children. Patches not licensed in UK. Licensed for the treatment of hypertension.

### *Therapeutics*

- Consider monitoring blood pressure and pulse on starting treatment and after each dose increase.
- Avoid abrupt discontinuation: risk of acute withdrawal symptoms including rebound hypertension.
- Can be administered by the buccal route. Some drug may be swallowed. This is unlikely to significantly affect the bioavailability but may delay the onset of action.
- Can be administered by continuous subcutaneous infusion for status dystonicus.
- Can be used as substitute for tizanidine if enteral route is unavailable due to similar mechanism of action although less hypotensive effect.
- Higher doses up to 200micrograms/kg/24hours via enteral, intravenous and transdermal routes have been reported in status dystonicus although sedation is a significant adverse effect.

### *Cautions*

- Caution in bradycardia, Raynaud's or other occlusive peripheral vascular disease.
- Remove patches before MRI scanning: risk of burns.

### *Side effects*

- Common side effects include constipation, nausea, dry mouth, vomiting, postural hypotension, dizziness, sleep disturbances, headache.

### *Interactions*

- Effects 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 blood pressure.

### *Pharmacokinetics*

- Oral, sublingual and rectal bioavailability 75-95%, although this may be lower in children. Generally 1:1 oral:sublingual:IV:SC:PR conversion can be used. Half-life 12-33 hours.
- Anecdotal reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4micrograms/kg have been used.
- Has also been administered via intranasal route using atomised injection solution using doses similar to oral route. Onset of action is faster than by mouth.
- Onset of action 30-60 minutes via oral, sublingual or rectal routes. Time to peak plasma concentration: oral 1.5-5 hours; epidural 20 minutes; transdermal, continuous intravenous and subcutaneous infusion 2-3 days.
- Considerable inter-individual variation in bioavailability of patches: caution when converting from other routes.

### *Hepatic impairment, renal impairment*

- Accumulates in renal impairment. Consider reducing dose if GFR less than 30ml/min/1.73m<sup>2</sup>

*Administration*

- Oral solution may be administered via an enteral feeding tube. Alternatively, tablets may be crushed and dispersed in water for administration via an enteral feeding tube. The 25microgram tablets do not appear to disperse in water as readily as the 100microgram tablets. IV solution may also be given via the enteral tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Injection can be administered by buccal or sublingual route. Alternatively oral tablets can be administered sublingually
- Rectal administration using parenteral preparation diluted to 10micrograms/ml with sodium chloride 0.9%
- Parenteral solution can be administered undiluted as a subcutaneous injection or diluted in sodium chloride 0.9% for continuous subcutaneous infusion. Can be combined with a number of other drugs commonly administered by continuous subcutaneous infusion in palliative care: consult appropriate specialist texts.

*Patient information*

- Patient information: see Medicines for Children leaflet: "Clonidine for Tourette's syndrome ADHD and sleep onset disorder"  
<https://www.medicinesforchildren.org.uk/medicines/clonidine-for-tourettes-syndrome-adhd-and-sleep-onset-disorder/>

*Available as*

- Tablets (25micrograms, 100micrograms), oral solution (50micrograms/5ml), injection (150 micrograms/ml), transdermal patch (available via importation company)
  - 2.5mg patch (=100 micrograms clonidine/day for 7 days)
  - 5mg patch (=200 micrograms clonidine/day for 7 days)
  - 7.5mg patch (= 300 micrograms clonidine/day for 7 days)

## Co-danthramer (dantron and poloxamer 188)

### Use:

- Constipation in end-of-life care

### Dose and route:

By mouth:

Co-danthramer 25/200 suspension 5ml = one co-danthramer 25/200 capsule (Dantron 25mg, poloxamer '188' 200mg):

- **Child 2-11 years:** 2.5–5ml at night
- **Child 6-11 years:** 1 capsule at night
- **12 years and over:** 5–10ml or 1–2 capsules at night.

Strong co-danthramer 75/1000 suspension 5ml = two strong co-danthramer 37.5/500 capsules:

- **12 years and over:** 5ml or 1–2 capsules at night.

### Notes:

- Stimulant laxative (dantron) combined with a wetting agent (poloxamer 188)

#### *Licensing*

- Licensed for terminally ill patients of all ages

#### *Side effects*

- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- Rodent studies indicate potential carcinogenic risk.
- Dantron can turn urine red/brown.

#### *Administration*

- Suspension can be used with enteral feeding tubes but is quite viscous, needing some pressure on syringe and to be flushed well after administration. Administration into the jejunum is unlikely to affect pharmacological response.

#### *Available as*

- Co-danthramer 25/200 suspension 5 ml = one co-danthramer 25/200 capsule (Dantron 25mg, poloxamer '188' 200mg), Strong co-danthramer 75/1000 suspension 5 ml = two strong co-danthramer 37.5/500 capsules.

## Co-danthrusate (dantron and docusate sodium)

### Use:

- Constipation in end-of-life care

### Dose and route:

By mouth:

Co-danthrusate 50/60 suspension 5ml = one co-danthrusate 50/60 capsule (Dantron 50mg/ Docusate sodium 60mg)

- **Child 6-11 years:** 5ml or 1 capsule at night
- **12 years and over:** 5–15ml or 1–3 capsules at night

### Notes:

- Stimulant laxative (dantron) combined with a softener (docusate sodium)

### *Licensing*

- Licensed for terminally ill patients of all ages

### *Therapeutics*

- Not recommended for under 6 years.

### *Side effects*

- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- Dantron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

### *Administration*

- No specific data on enteral tube administration are available for this preparation. If necessary use the suspension and flush tube well after use. Consider diluting with water to aid administration.

### *Available as*

- Co-danthrusate 50/60 suspension 5ml = one co-danthrusate 50/60 capsule (Dantron 50mg/ Docusate sodium 60mg)

## **Codeine Phosphate**

Codeine is no longer indicated for palliative care in children. It has been replaced by other opioids, particularly oral morphine and buccal diamorphine or fentanyl.



## Cyclizine

### Use:

- Antiemetic of choice for raised intracranial pressure.
- Nausea and vomiting of vestibular origin or where other antiemetics (metoclopramide, 5HT<sub>3</sub> antagonists) have failed.

### Dose and route:

By mouth or by slow intravenous injection over 3–5 min:

- **Child 1 month- 5 years:** 500micrograms–1mg/kg up to 3 times daily, maximum single dose 25mg
- **Child 6-11 years:** 25mg up to 3 times daily
- **12 years and over:** 50mg up to 3 times daily

By rectum:

- **Child 2- 5 years:** 12.5mg up to 3 times daily
- **Child 6-11 years:** 25mg up to 3 times daily
- **12 years and over:** 50mg up to 3 times daily

By continuous intravenous or subcutaneous infusion:

- **Child 1-23 months:** 1.5-3mg/kg/24hours (maximum 25mg/24hours),
- **Child 2-5 years:** 25-50mg/24hours
- **Child 6-11 years:** 37.5-75mg/24hours
- **12 years and over:** 75-150mg/24hours

### Notes:

- Antihistaminic, antimuscarinic antiemetic.

#### *Licensing*

- Tablets are not licensed for use in children under 6 years old. Injection is not licensed for use in children.

#### *Therapeutics*

- Injection solution has also been given sublingually in adults using same doses as oral or rectal routes.
- Anticholinergic effects reduce effect of prokinetic antiemetics e.g. domperidone, metoclopramide

*Contraindications, cautions*

- Avoid in severe cardiac failure: may cause fall in cardiac output.
- Increased risk of transient paralysis with intravenous use in patients with neuromuscular disorders.

*Side effects*

- Antimuscarinic side effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Risk of site reactions when administered via SC or IV route
- Rapid SC or IV bolus can lead to 'light-headedness': disliked by some but enthralling to others leading to repeated requests for IV cyclizine.

*Pharmacokinetics*

- Some evidence suggests 50% oral bioavailability: consider reducing dose when converting oral to IV or SC routes.
- May accumulate with continued use.

*Hepatic impairment, renal impairment*

- Avoid in severe liver disease.

*Interactions*

- Increased sedative and antimuscarinic effect when given with tricyclics, anxiolytics, MAOI's.

*Administration*

- For continuous subcutaneous or intravenous infusion, dilute only with water for injection or 5% dextrose: *incompatible* with 0.9% sodium chloride causing precipitation.
- Concentration dependent *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. Alternatively use oral suspension. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Tablets (50mg), suppositories (12.5mg, 25mg, 50mg, 100mg from 'specials' manufacturers) and injection (50mg/ml). Oral suspension unlicensed special (50mg/5ml Nova Laboratories, 5mg/5ml). Alternative suppliers may also be available.

## Dantrolene

### Use:

- Skeletal muscle relaxant
- Chronic severe skeletal muscle spasm or spasticity

### Dose and route:

Doses should be increased *slowly*

By mouth:

- **Child 5-11 years:** Initial dose of 500micrograms/kg once daily; increase after 7 days to 500micrograms/kg/dose 3 times daily. Increase every 7 days by a further 500micrograms/kg/dose until response

Maximum recommended dose 2mg/kg 3–4 times daily, maximum total daily dose 400mg

- **12 years and over:** Initial dose of 25mg once daily; increase after 7 days to 25mg 3 times daily. Increase by a further 500micrograms/kg/dose every 7 days until response.

Maximum recommended dose 2mg/kg 3–4 times daily, maximum total daily dose 400mg

### Notes:

#### *Licensing*

- Not licensed for use in children.

#### *Therapeutics*

- Acts directly on skeletal muscle so can be used concurrently with baclofen and diazepam.

#### *Contraindications, cautions*

- Caution in patients impaired cardiac or pulmonary function.

#### *Side effects*

- Risk of hepatotoxicity; consider checking liver function before and at regular intervals during therapy.
- Pericarditis, pleural effusion, respiratory depression, exacerbation of cardiac insufficiency, tachycardia and blood pressure changes, drowsiness, dizziness, weakness, nausea and diarrhoea.

#### *Hepatic impairment, renal impairment*

- Contraindicated in hepatic impairment: avoid in liver disease or concomitant use of hepatotoxic drugs.

*Administration*

- Capsules can be opened and dispersed in water for administration via gastrostomy. Alternatively use oral suspension.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Capsules (25mg, 100mg), oral suspension (extemporaneous formulation 5mg/ml).

## Dexamethasone

### Use:

- Headache associated with raised intracranial pressure caused by a tumour
- Malignant spinal cord compression
- Reduction of symptoms due to peri-tumour oedema and inflammation
- Neuropathic pain due to nerve compression
- Bone pain due to malignant infiltration
- Antiemetic either as an adjuvant or in highly emetogenic cytotoxic therapies

### Dose and route:

#### Headache associated with raised intracranial pressure, spinal cord compression

By mouth or short intravenous infusion over 15-20 minutes:

- **Child 1 month- 11 years:** 250micrograms/kg twice daily for 5 days; then stop
- **12 years and over:** 8mg twice daily (or 16mg once daily) for 5 days, then stop

If symptoms recur consider a further pulse of dexamethasone followed by a washout period to reduce side effects. Reduce to the minimum effective dose if discontinuation is not possible.

Prescribe injection or infusion as dexamethasone *base*.

Higher doses may be advised particularly in malignant spinal cord compression.

Once and twice daily doses to be given before midday to reduce likelihood of corticoid induced insomnia

#### Reduction of symptoms due to peri-tumour oedema and inflammation

#### Neuropathic pain due to malignant nerve compression

#### Bone pain due to malignant infiltration

By mouth, short intravenous infusion over 15–20 minutes, or subcutaneous injection

- **Child under 1 year:** Initial dose 250micrograms once or twice daily.
- **1- 5 years:** Initial dose 1mg once or twice daily.
- **6-11 years:** Initial dose 2mg once or twice daily.
- **12 years and over:** 4mg once or twice daily.

Initial therapy for 2–5 days then stop.

If symptoms recur consider a further pulse of dexamethasone followed by a washout period to reduce side effects. Reduce to the minimum effective dose if discontinuation is not possible.

Prescribe injection or infusion as dexamethasone *base*.

Once and twice daily doses to be given before midday to reduce likelihood of corticoid induced insomnia

### Antiemetic

By mouth, short intravenous infusion over 15-20 minutes, or subcutaneous injection:

- **Child under 1 year:** Initial dose 250micrograms 3 times daily. This dose may be increased as necessary and as tolerated up to 1mg 3 times daily
- **1-5 years:** Initial dose 1mg 3 times daily. This dose may be increased as necessary and as tolerated up to 2mg 3 times daily
- **6-11 years:** Initial dose 2mg 3 times daily. This dose may be increased as necessary and as tolerated up to 4mg 3 times daily
- **12 years and over:** 4mg 3 times daily

Prescribe injection or infusion as dexamethasone *base*.

### Notes:

#### *Licensing*

- Not licensed for use in children as an anti-emetic.

#### *Therapeutics*

- High glucocorticoid activity but relatively insignificant mineralocorticoid activity.
- Dexamethasone 1mg = 7mg prednisolone, anti-inflammatory equivalence.
- Prescribe injection or infusion as dexamethasone *base* i.e. as “dexamethasone”, not “dexamethasone phosphate” or “dexamethasone sodium phosphate”.
- Long duration of action. Can be given in a single daily dose each morning for most indications. Administration of the daily dose of dexamethasone before midday reduces the likelihood of corticosteroid induced insomnia and agitation.
- Adverse effects quickly outweigh the benefits: use short courses wherever possible or reduce as quickly as possible to lowest effective dose.
- Can be stopped abruptly if given for less than two weeks. Doses should be weaned gradually over several weeks for longer courses in order to allow recovery of the hypothalamic-pituitary axis and avoid Addisonian crisis.
- Dexamethasone (base) 1mg = dexamethasone phosphate 1.2mg = dexamethasone sodium phosphate 1.3mg.

#### *Side effects*

- Rapid injection can cause paraesthesia and cardiovascular collapse.
- Problems of body-weight gain and Cushingoid appearance are major concerns specifically in children.
- Other side effects include: diabetes, hypertension, osteoporosis, muscle wasting, peptic ulceration and behavioural problems and agitation, also extreme exacerbation of and lability of mood (tearfulness, physical aggression), hypokalaemia.

- Consider the use of proton pump inhibitor (PPI) to prevent gastrointestinal irritation.
- Some injection formulations may contain latex: consult SPC.

*Pharmacokinetics*

- Oral bioavailability >80%; 1:1 oral:IV:SC conversion can be used.

*Interactions*

- Moderate inducer of cytochrome P450 enzyme CYP3A4. May reduce levels of drugs that are metabolised by this enzyme.
- Also metabolised by CYP3A. Levels increased by drugs that inhibit this enzyme including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine and phenobarbital.

*Administration*

- 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.
- Alkaline drug: increased risk of precipitation when used in combination with other drugs in a syringe driver.

*Patient information*

- See Medicines for Children Leaflet "Dexamethasone for croup"  
<https://www.medicinesforchildren.org.uk/medicines/dexamethasone-for-croup/>

*Available as*

- Tablets (500 micrograms, 2mg, 4mg), soluble tablets (2mg, 4mg, 8mg, 10mg, 20mg) oral solution (2mg/5ml 10mg/5ml and 20mg/5ml) and injection dexamethasone base 3.8mg/ml and 3.3mg/ml.

## Diamorphine

### Use:

- Moderate to severe pain
- Breakthrough pain where oral route is not available, or rapid onset of action is required
- Dyspnoea
- Alternative opioid where large doses need to be administered in small volume

Important safety information

#### For all opioids

#### MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The **APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### Pain in patients already receiving regular strong opioids

By continuous subcutaneous or intravenous infusion

Calculate dose of diamorphine by using oral morphine equivalent (OME) from previous analgesia (See table Appendix 1).

Approximate equianalgesic ratios for oral and intravenous morphine and diamorphine

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Diamorphine CSCI or CIVI	6:1	Divide 24hour morphine dose by 6	Morphine oral 30mg/24hours ÷ 6 = diamorphine CSCI 5mg/24hours
Morphine CSCI or CIVI	Diamorphine CSCI or CIVI	2:1	Divide 24hour morphine dose by 2	Morphine CSCI 20mg/24hours ÷ 2 = diamorphine CSCI 10mg/24hours



**Breakthrough pain in patients already receiving opioids**

Review background analgesia if breakthrough analgesia is required more than twice in a 24-hour period.

By subcutaneous or intravenous routes

- 1/10 to 1/6 (10-16%) of 24-hour diamorphine infusion every 1-4 hours as needed.

By intranasal or buccal route

Approximate equianalgesic ratios for intranasal or buccal diamorphine

Conversion		Ratio	Calculation	Example
From	To			
Diamorphine CIVI or CSCI	Intranasal or buccal diamorphine	1:2	<p><b>Multiply</b> 24hour diamorphine dose by 2</p> <p><i>Then</i> administer 1/10-1/6 every 1- 4 hours as needed</p>	<p>Diamorphine 20mg/24hours  <math>\times 2 = 40</math>  <math>40 \div 10 = 4</math>  <math>40 \div 6 = 6.6</math>            Breakthrough dose = 4-6.6mg intranasal diamorphine</p>
Oral morphine	Intranasal or buccal diamorphine	3:1	<p>Divide 24hour morphine dose by 3</p> <p><i>Then</i> administer 1/10-1/6 every 1- 4 hours as needed</p>	<p>Morphine oral 30mg/24hours  <math>\div 3 = 10</math>  <math>10 \div 10 = 1</math>  <math>10 \div 6 = 1.7</math>            Breakthrough dose = 1-1.7mg intranasal diamorphine</p>
Morphine CIVI or CSCI	Intranasal or buccal diamorphine	1:1	<p>Administer 1/10-1/6 24hour morphine dose every 1- 4 hours as needed</p>	<p>Morphine CIVI 60mg/24hours  <math>60 \div 10 = 6</math>  <math>60 \div 6 = 10</math>            Breakthrough dose = 6-10mg intranasal diamorphine</p>

## Pain in opioid naive patients

Doses refer to **starting** doses only<sup>21</sup>

Age range	Intranasal or buccal	Intravenous or subcutaneous bolus	Intravenous or subcutaneous infusion/24hours
<b>Neonate</b>	40micrograms/kg/dose 6 hourly	20micrograms/kg/dose 6 hourly	80micrograms/kg/24hours
<b>1- 2 months</b>	60micrograms/kg/dose 6 hourly	30micrograms/kg/dose 6 hourly	120micrograms/kg/24hours
<b>3- 5 months</b>	60micrograms/kg/dose 4 hourly	30micrograms/kg/dose 4 hourly	180micrograms/kg/24hours
<b>6- 23 months</b>	80micrograms/kg/dose 4 hourly	40micrograms/kg/dose 4 hourly	240micrograms/kg/24hours
<b>2-11 years</b>	80-100micrograms/kg maximum 5mg/dose 4 hourly	40micrograms/kg maximum 2.5mg/dose 4 hourly	240- 300micrograms/kg/24hours maximum 10mg/24hours
<b>12 years and over</b>	80-100micrograms/kg maximum 5mg/dose 4 hourly	40- 50micrograms/kg/dose 4 hourly maximum 2.5mg/dose  <i>Alternatively</i> 1.25-2.5mg/dose	240micrograms/kg/24hours maximum 15mg/24hours

Injection solution can be used by intranasal or buccal routes. A Mucosal Atomiser Device (MAD) can be used for accuracy of administration.

## Dyspnoea

By buccal, intranasal, subcutaneous or intravenous routes

- **Child 1 month and over:** 25-50% of pain doses

## Notes:

- Pro-drug of morphine.

### Licensing

- Licensed for the treatment of children who are terminally ill.

### Therapeutics

- Morphine is normally considered strong opiate of first choice by mouth and for intravenous infusion or continuous subcutaneous infusion. Only benefit of diamorphine via these routes is greater solubility when high doses are required.
- Has been used via intravesical route for bladder spasms and topically in Intra-Site gel for painful skin ulcers (unlicensed indications).
- Refer to Principles of Opioid Stewardship, Appendix 2

<sup>21</sup> Doses adapted from BNFC ensuring age bands and dosing intervals are consistent, including extrapolating from morphine, taking into account longer half-life in neonates and infants, bio-availability via different routes, and ensuring consistent total daily dose across each age band

- Ensure access to an appropriate stimulant laxative if administered regularly

*Pharmacokinetics*

- No data directly comparing intranasal with buccal route in children. Bioavailability may be lower for buccal administration particularly if larger volumes are used for administration and some of the drug is swallowed.
- Bioavailability may be affected by developmental changes in nasal anatomy in the neonatal period and infancy

*Hepatic impairment, renal impairment*

- Increase dosing interval, reduce dose and administer as required rather than regularly in renal impairment. Avoid in severe renal impairment.
- Caution in hepatic impairment: consider reducing dose.

*Administration*

- Injection powder can be diluted in water for injection for intranasal or buccal administration (unlicensed route of administration).
- Can be given by subcutaneous infusion up to a concentration of 250mg/ml. Dilute with water for injections for CSCI: concentration-related incompatibility with 0.9% sodium chloride at concentrations above 40mg/ml.

*Available as*

- Injection (5mg, 10mg, 30mg, 100mg, 500mg ampoules). Supplies may be limited

*CD*

- CD Schedule 2.

## Diazepam

### Use:

- Anxiety, including anxiety associated with dyspnoea, panic attacks
- Agitation
- Relief of muscle spasm or dystonia
- Status epilepticus

Important safety information

#### **For all benzodiazepines**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### **Short term anxiety relief, panic attacks and agitation**

By mouth:

- **Child 2-11 years:** 500micrograms-2mg 3 times daily
- **12 years and over:** Initial dose of 2mg 3 times daily increasing as necessary and as tolerated to a maximum of 10mg 3 times daily.

#### **Relief of muscle spasm, dystonia (as rescue or short-term therapy)**

By mouth:

- **Child 1-11 months:** Initial dose of 250micrograms/kg twice daily
- **1-4 years:** Initial dose of 2.5mg twice daily
- **5-11 years:** Initial dose of 5mg twice daily
- **12 years and over:** Initial dose of 10mg twice daily; maximum total daily dose 40mg.

## Status epilepticus

By intravenous 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 10mg) repeated once after 10 minutes if necessary
- **12 years and over:** 10mg repeated once after 10 minutes if necessary.

By rectum (rectal solution):

- **Neonate:** 1.25–2.5mg repeated once after 10 minutes if necessary
- **Child 1 month–1 year:** 5mg repeated once after 10 minutes if necessary
- **2–11 years:** 5–10mg repeated once after 10 minutes if necessary
- **12 years and over:** 10–20mg repeated once after 10 minutes if necessary.

## Notes:

### *Licensing*

- Rectal tubes not licensed for children under 1 year old.

### *Contraindications, cautions*

- Avoid in acute or severe respiratory insufficiency unless in the imminently dying.
- Caution in muscle weakness, respiratory depression, or sleep apnoea.

### *Side effects*

- Dose-dependent drowsiness and impaired psychomotor and cognitive skills.

### *Pharmacokinetics*

- Almost 100% bioavailable when given orally or by rectal solution.
- Onset of action: approximately 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. The active metabolite, nordiazepam, has a plasma half-life of 48–120 hours.

### *Hepatic impairment, renal impairment*

- Caution in hepatic impairment

### *Interactions*

- Metabolised by cytochrome P450 enzymes CYP2C19 and CYP3A4. Levels increased by drugs that inhibit these enzymes including erythromycin, fluconazole, fluoxetine, and omeprazole. Levels decreased by drugs that induce these enzymes including carbamazepine and phenobarbital.
- Risk of enhanced CNS depressant effect if co-administered with other CNS depressants including neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates or sedative antihistamines.

*Administration*

- The oral solution may be administered via a gastrostomy tube. Dilute with water before administration to reduce viscosity. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.

*Patient information*

- See Medicines for Children leaflet “Diazepam for muscle spasm.”  
<https://www.medicinesforchildren.org.uk/medicines/diazepam-for-muscle-spasm/> and  
“Diazepam (rectal) for stopping seizures”  
<https://www.medicinesforchildren.org.uk/medicines/diazepam-rectal-for-stopping-seizures/>

*Available as*

- Tablets (2mg, 5mg, 10mg), oral solution/suspension (2mg/5ml, 5mg/5ml), rectal tubes (5mg, 10mg), and injection (5mg/ml solution and 5mg/ml emulsion)

*CD*

- CD Schedule 4 part 1

## Diclofenac Sodium

### Use:

- Mild to moderate pain and inflammation
- Musculoskeletal pain

### Dose and route:

By mouth or rectum:

- **Child 6 months and over** : Initial dose of 300microgram/kg 3 times daily increasing if necessary to a maximum of 1mg/kg 3 times daily (maximum 50mg single dose).

By intermittent intramuscular injection or intravenous infusion (using Voltarol® injection):

- **Child 2 years and over:** 300-500microgram/kg 1-2 times daily  
Increase, if required, to maximum 1mg/kg 1–2 times daily or 150mg/day, for a maximum of 2 days (see notes below)

### Notes:

- Peripheral and central preferential COX 2 inhibitor

### Licensing

- 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 25mg not licensed for use in children; injection licensed for short term use (up to 2 days) in adults only

### Therapeutics

- Maximum intravenous and intramuscular doses quoted above refer primarily to short term use in post-operative pain. Use lower doses if longer term parenteral use is required.
- Higher doses may have a ceiling effect risking increased adverse effects, particularly with longer term use, without additional analgesic effect.

### Contraindications, cautions

- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

### Side effects

- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The

greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.

- All NSAIDs are associated with serious gastro-intestinal toxicity. Diclofenac is associated with an intermediate risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.

*Pharmacokinetics*

- Oral bioavailability approximately 30-50%, rectal bioavailability approximately 50%

*Interactions*

- Metabolised by cytochrome P450 enzyme CYP2C9. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine

*Administration*

- Smallest dose that can be given practically by rectal route is 3.125mg by cutting a 12.5mg suppository into quarters.
- The Palliative Care Formulary describes unlicensed CSCI use at 50% oral dose, with 0.9% sodium chloride as diluent.
- For IV infusion, dilute with 100-500ml of sodium chloride 0.9% or glucose 5%. Buffer the diluent with sodium bicarbonate (0.5ml of 8.4% or 1ml of 4.2%). Administer over 30 minutes-2 hours.
- Use oral suspension for administration via a feeding tube. There should be no reduction in bioavailability from jejunal administration.

*Patient information*

- See Medicines for Children leaflet "Diclofenac for pain and inflammation"  
<https://www.medicinesforchildren.org.uk/medicines/diclofenac-for-pain-and-inflammation/>

*Available as*

- Gastro-resistant tablets (25mg, 50mg), modified-release tablets (25mg, 50mg, and 75mg), modified release capsules (75mg and 100mg), injection (25mg/ml Voltarol® , licensed in adults for IV **infusion** and IM bolus only, and 75mg/ml Akis®, licensed in adults for IV, IM or SC **bolus** only), and suppositories (12.5mg, 25mg, 50mg and 100mg). Oral suspension 50mg in 5ml available as an unlicensed 'special'



## **Dihydrocodeine**

Dihydrocodeine is no longer indicated for palliative care in children. It has been replaced by other opioids, particularly oral morphine and buccal diamorphine or fentanyl.

## Docusate

### Use:

- Constipation

### Dose and route

By mouth:

- **Child 6 months-1 year:** Initial dose of 12.5mg 3 times daily; adjust dose according to response
- **Child 2-11 years:** Initial dose of 12.5mg 3 times daily. Increase to 25mg 3 times daily as needed. Adjust dose according to response.
- **12 years and over:** Initial dose 100mg 3 times daily. Adjust as needed according to response up to 500mg/day in divided doses

By rectum:

- **12 years and over:** 1 enema (120mg) as single dose

### Notes:

Emulsifying, wetting and mild stimulant laxative

#### *Licensing*

- Adult oral solution and capsules not licensed in children < 12 years.

#### *Therapeutics*

- Generally a more powerful stimulant laxative than docusate is required for opioid induced constipation
- Oral preparations act within 1–2 days.
- Rectal preparations act within 20mins and may cause a mild localised 'burning' sensation.
- Recommended doses may be exceeded on specialist advice.

#### *Administration*

- For administration by mouth, solution may be mixed with milk or squash to disguise the unpleasant taste. Oral solution may be administered via an enteral feeding tube. Administration directly into the jejunum will not affect the pharmacological response.

#### *Available as*

- Capsules (100mg), oral solution (12.5mg/5ml paediatric, 50mg/5ml adult, 100mg/5ml adult), and enema (120mg in 10g single dose pack).

## Domperidone

### Use:

- Nausea and vomiting where poor GI motility is the cause
- Gastro-oesophageal reflux resistant to other therapy

#### Important safety information

#### **MHRA/CHM advice (updated December 2019): Domperidone for nausea and vomiting: lack of efficacy in children; reminder of contraindications in adults and adolescents**

Domperidone is no longer indicated for the relief of nausea and vomiting in children aged under 12 years or those weighing less than 35 kg. A European review concluded that domperidone is not as effective in this population as previously thought and alternative treatments should be considered. Healthcare professionals are advised to adhere to the licensed dose and to use the lowest effective dose for the shortest possible duration (max. treatment duration should not usually exceed 1 week).

The use of domperidone in palliative care is excluded from these recommendations HOWEVER caution should be exercised nevertheless.

- Use the minimum effective dose.
- Avoid in known cardiac problems or other risk factors.
- Consider monitoring QTc before initiating treatment and with dose increases

### Dose and route:

By mouth:

- **Neonate:** 250micrograms/kg 3 times daily. Increase if necessary to 400micrograms/kg 3 times daily
- **Child over 1 month- 11 years:** Initial dose of 250micrograms/kg, maximum 10mg/dose, 3 times daily. Dose may be increased if necessary to 400micrograms/kg 3-4 times daily, maximum 80mg in 24 hours
- **12 years and over:** Initial dose of 10mg 3–4 times daily before food. Dose may be increased, if necessary, to 20mg 3-4 times daily, maximum 80mg in 24 hours.

### Notes:

#### *Licensing*

- Not licensed for use in gastro-intestinal stasis, not licensed for use in children for gastro-oesophageal reflux disease.

### *Therapeutics*

- Reduced ability to cross blood brain barrier: less likely to cause extrapyramidal side effects compared with metoclopramide.
- Promotes gastrointestinal motility: diarrhoea can be an unwanted (or useful) side effect.
- Doses quoted reflect previously authorised maximum doses. Authorised doses have been since reduced due to concern regarding possible cardiac adverse effects. However benefits of higher doses may outweigh the risks in refractory symptoms in paediatric palliative care where safer alternative prokinetics are not available, and risk of cardiac adverse effects is relatively low.
- Prokinetic effect may be reduced by anticholinergic drugs including antiemetics e.g. cyclizine

### *Contraindications, cautions*

- Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Contraindicated in cardiac disease and in conditions where cardiac conduction is, or could be, impaired

### *Side effects*

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended.

### *Hepatic impairment, renal impairment*

- Avoid in hepatic impairment.

### *Interactions*

- Avoid in patients receiving other medications known to prolong QT-interval (e.g. erythromycin, ketoconazole).
- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including erythromycin and fluconazole.

### *Patient information:*

- See Medicines for Children leaflet: “Domperidone for gastro-oesophageal reflux”  
<https://www.medicinesforchildren.org.uk/medicines/domperidone-for-gastro-oesophageal-reflux/>

### *Administration*

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 (10mg), oral suspension (5mg/5 ml).

## Erythromycin

### Use:

- Antibiotic typically used in respiratory tract infections, and skin infections
- Gastrointestinal stasis (motilin receptor agonist) is the main indication in palliative care

### Dose and route:

#### Antibiotic

##### By mouth

- **Neonate:** 12.5mg/kg every 6 hours.
- **Child 1-23 months:** 125mg 4 times daily, increased to 250mg 4 times daily in severe infections. Total daily dose may be given in two divided doses
- **2-7 years:** 250mg 4 times daily, increased to 500mg 4 times daily in severe infections. Total daily dose may be given in two divided doses
- **8 years and over:** 250–500mg 4 times daily, increased to 500mg–1g 4 times daily in severe infections. Total daily dose may be given in two divided doses

##### By intravenous infusion

- **Neonate:** 10–12.5mg/kg every 6 hours
- **Child 1 month-11 years:** 12.5mg/kg, maximum 1g, every 6 hours
- **12 years and over:** 6.25mg/kg every 6 hours, for mild infections when oral treatment not possible, increased to 12.5mg/kg, maximum 1g, every 6 hours in severe infections

#### Prokinetic

##### By mouth or intravenous infusion

- **Neonate, child:** 3 mg/kg 4 times a day

Benefit is often seen at lower doses. Increase if necessary and as tolerated to a maximum of 1g 4 times daily

### Notes:

#### *Licensing*

- Not licensed for use in children with gastrointestinal stasis

#### *Contraindications, cautions*

- Contraindicated in patients with known clostridium difficile colonisation

- Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Prokinetic effect may be reduced by anticholinergic drugs including antiemetics e.g. cyclizine

#### *Side effects*

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in hepatic impairment or co-administration of potentially hepatotoxic drugs
- Associated with increased risk of hypertrophic pyloric stenosis in neonates and infants
- Risk of tachyphylaxis: start at lower doses where possible
- Increased risk of antibiotic associated colitis

#### *Interactions*

- Inhibitor of cytochrome P450 enzyme CYP3A4. Increases levels of drugs that are metabolised by this enzyme including alfentanil, buprenorphine, carbamazepine (also reducing erythromycin levels), dexamethasone, diazepam, domperidone, fentanyl and midazolam. This list is not exhaustive-see advice.
- Also metabolised by CYP3A4. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine (also increasing carbamazepine levels).

#### *Administration*

- Dilute the suspension with an equal volume of water before administration via enteral feeding tubes. Absorbed in small intestine

#### *Patient information*

- See Medicines for Children leaflet "Erythromycin for treating bacterial infections" <https://www.medicinesforchildren.org.uk/medicines/erythromycin-for-bacterial-infections/>

#### *Available as*

- Tablets (250mg, 500mg) and gastro-resistant tablets (250mg, 500mg) and oral suspension (125mg/5ml, 250mg/5ml, 500mg/5ml). Also available as 1g powder for solution for infusion.

## Etoricoxib

### Use:

- Anti-inflammatory analgesic
- Musculoskeletal pain

### Dose and route:

By mouth:

- **Child 12-15 years:** Initial dose of 30mg once daily. Increased as necessary and as tolerated to a maximum of 60mg once daily
- **16 years and over:** Usual dose of 30-60mg once daily. Doses of 90mg daily may be used on a short term basis.

### Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.

#### *Licensing*

- Not licensed for use in children less than 16 years of age. No pharmacokinetic data in children less than 12 years of age

#### *Therapeutics*

- No difference in tolerability or efficacy has been shown between the selective cox-2 inhibitors (etoricoxib, celecoxib) and the non-selective NSAID, naproxen.
- Doses up to 120mg have been used on a short term basis in acute gouty arthritis in adults.

#### *Contraindications, cautions*

- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID. Etoricoxib may be better tolerated than other NSAIDs in patients with known hypersensitivity.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

#### *Side effects*

- All NSAIDs are associated with serious gastro-intestinal toxicity. Etoricoxib is associated with low risk of gastro-intestinal toxicity . Consider prescription of a proton pump inhibitor with prolonged use.
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.
- Common adverse events (1-10% patients): 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; increased hepatic transaminases (ALT, AST); ecchymosis; asthenia/fatigue, flu-like disease.

*Hepatic and renal impairment*

- Contraindicated in severe hepatic and severe renal impairment

*Interactions*

- 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 enzymes. 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.

*Administration*

- Etoricoxib tablets may be dispersed in 10ml 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. Particles of the film coat may remain; flush well. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Film coated tablets 30mg, 60mg, 90mg, 120mg.



## Famotidine (NEW)

### Use:

- Histamine H<sub>2</sub> antagonist to inhibit / reduce gastric acid secretion
- Episodic dyspepsia
- Gastro-oesophageal reflux disease
- Prevention and treatment of peptic ulceration

### Dose and route:

By mouth

#### Gastro-oesophageal reflux disease

- **Neonate-3 months:** 500micrograms/kg/dose once daily, increased to 1mg/kg/dose once daily if necessary
- **Child 3 months and older:** initial dose 500micrograms/kg/dose twice daily, increasing to 1mg/kg/dose twice daily if required, maximum single dose 40mg

#### Peptic Ulceration

- **Child 1 year and older:** 500micrograms/kg once daily at night or in 2 divided doses, maximum 40mg/day

### Notes:

- Histamine H<sub>2</sub> antagonist, reduces gastric acid secretion.

#### *Licensing*

- Not licensed for use in children in the UK. Licensed for all ages for gastro-oesophageal reflux disease, and from 1 year of age for peptic ulcer disease in the USA. Limited information of use in neonates.

#### *Therapeutics*

- No prokinetic effect, unlike ranitidine

#### *Caution*

- Increased incidence of NEC in neonates, especially very low birthweight.
- Use of gastric acid inhibitors, including proton pump inhibitors and H<sub>2</sub> blockers, has been associated with an increased risk for development of acute gastroenteritis and community-acquired pneumonia.
- Consider monitoring blood counts and liver function in long term use.
- Continue treatment for some time after symptom relief in peptic ulcer disease.

*Side effects*

- Constipation; diarrhoea; dizziness; fatigue; headache; myalgia; skin reactions; confusion; agitation; decreased appetite; dry mouth; taste altered; vomiting.

*Renal Impairment*

- Reduce dose by 50% in severe renal impairment.

*Pharmacokinetics*

- Duration of effect: 10-12 hours, oral bioavailability: 40-50%.

*Drug Interactions*

- No clinically important pharmacokinetic drug interactions.
- Increase in gastric pH may decrease the bioavailability of certain drugs (e.g. ketoconazole, itraconazole).
- Concomitant use of antacids or sucralfate may reduce absorption of famotidine: administer antacids at least an hour and sucralfate at least 2 hours after famotidine.

*Administration*

- Oral: Tablets may be taken with or without food. Tablets can be crushed and mixed with water to aid oral administration (off-label). Without crushing famotidine tablets will disperse in two to five minutes.
- Enteral Feeding Tube: There is no information on administration of famotidine tablets or suspension via an enteral feeding tube. Use of suspension likely to be preferable. Consider dilution if necessary to reduce viscosity and aid administration.
- Injection (available in the USA) can be given intravenously as a slow bolus or short infusion. Has also been given as a subcutaneous bolus or continuous subcutaneous infusion.
- Single case series reporting rectal administration at a dose of 1mg/kg.

*Available as*

- UK: 20mg and 40mg film-coated tablets, a suspension may be available from UK 'specials' manufacturers; extemporaneous formulation for oral suspension available.
- US (available for importation): 10mg, 20mg and 40mg film-coated tablets and oro-dispersible wafers; 40mg in 5ml oral suspension; 10mg/ml injection concentrate.

## Fentanyl

### Use:

- Moderate to severe pain
- Transdermal fentanyl should NOT be used in opioid naive patients

Important safety information

#### **For all opioids**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

## Dose and route:

### **Stable Pain in patients already receiving regular strong opioids**

By transdermal patch

Important safety information

**MHRA/CHM advice: Transdermal fentanyl patches for non-cancer pain: do not use in opioid naive patients (September 2020)**

Fentanyl is a potent opioid: a 12 micrograms per hour fentanyl patch equates to daily doses of oral morphine of approximately 30mg daily

#### **Do NOT use fentanyl patches in opioid naive patients**

Use other analgesics and other opioid medicines (opioids) for non-cancer pain before prescribing fentanyl patches

If prescribing fentanyl patches, remind patients or their carers of the importance of:

- Not exceeding the prescribed dose
- Following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application
- Not cutting patches and avoiding exposure of patches to heat including via hot water (bath, shower)
- Ensuring that old patches are removed before applying a new one
- Following instructions for safe storage and properly disposing of used patches or patches that are not needed. It is particularly important to keep patches out of sight and reach of children at all times
- Make patients and caregivers aware of the signs and symptoms of fentanyl overdose and advise them to seek medical attention immediately (by dialling 999 and requesting an ambulance) if overdose is suspected
- Remind patients that long-term use of opioids in non-cancer pain (longer than 3 months) carries an increased risk of dependence and addiction, even at therapeutic doses (see Drug Safety Update on risk of dependence and addiction with opioids); before starting treatment with opioids, agree with the patient a treatment strategy and plan for end of treatment

Report suspected adverse drug reactions, including dependence, accidental exposure, or overdose associated with fentanyl patches, via the Yellow Card scheme

Convert using oral morphine equivalent (OME) from previous opioid analgesia see Appendix 1. NOT to be used in opioid naive patients. Not suitable for dose titration in patients with unstable pain.

72 hour Fentanyl patches are *approximately* equivalent to the following 24 hour doses of oral morphine

Oral morphine 30mg/24hours	≡	Fentanyl 12micrograms/hour
Oral morphine 60mg/24hours	≡	Fentanyl 25micrograms/hour
Oral morphine 120mg/24hours	≡	Fentanyl 50micrograms/hour
Oral morphine 180mg/24hours	≡	Fentanyl 75micrograms/hour
Oral morphine 240mg/24hours	≡	Fentanyl 100micrograms/hour

Consider reducing the dose of fentanyl by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Systemic analgesic concentrations are generally reached within 12–24 hours after applying the first patch. If converting from:

- 4-hourly oral morphine: administer regular morphine doses for the first 12 hours after applying the patch.
- 12-hourly slow release morphine: apply the patch and administer 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 morphine infusion: continue the infusion for 8- 12 hours after applying the patch.

### **Pain in patients already receiving regular strong opioids**

By continuous intravenous or subcutaneous infusion

Convert using oral morphine equivalent (OME) from previous opioid analgesia, see Appendix 1

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Fentanyl CSCI or CIVI	100:1	Divide 24hour morphine dose by 100 to give fentanyl dose in <i>mg/24hours</i>  Then multiply fentanyl dose in mg/24hours by 1000 to convert to <i>micrograms/24hours</i>	Morphine oral 60mg/24hours ÷ 100 = 0.6mg/24hours CIVI fentanyl  Fentanyl 0.6mg/24hours x 1000 = 600micrograms/24hours

Consider reducing the dose of fentanyl by 25-50% when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

### **Breakthrough Pain in patients already receiving regular strong opioids**

By buccal or intranasal administration of injection solution

- 1/10 to 1/6 of the total CSCI or CIVI dose as required, up to hourly

There is no direct correlation between the effective PRN dose and the regular background dose: start with low dose and titrate according to response

Maximum dose limited to 50micrograms/1ml via the intranasal route and 100micrograms/2ml via buccal route due to available concentration of injection solution (50micrograms/ml).

Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

By oromucosal application (lozenge with oromucosal applicator), buccal lozenge, buccal tablet, commercially manufactured intranasal spray

- Dose must be titrated against patient's pain. Consult product literature.

Unlikely to be appropriate for patients receiving less than 60mg oral morphine or oral morphine equivalent per 24 hours

### **Pain in opioid naive patients**

By continuous intravenous or subcutaneous infusion

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate-11months:** 0.15-0.5micrograms/kg/hour (= 3.6-12micrograms/kg/24hours)
- **Child 1 year and over:** 0.25-1micrograms/kg/hour, maximum 50micrograms/hour (6-24micrograms/kg/24hours, maximum 1.2mg/24hours)

By buccal or intranasal administration of injection solution

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate- 11 months:** 1microgram/kg as a single dose
- **Child 2 years and over:** 1-2micrograms/kg as a single dose, with initial maximum single dose of 50micrograms

Maximum dose limited to 50micrograms/1ml via the intranasal route and 100micrograms/2ml via buccal route due to available concentration of injection solution (50micrograms/ml).

By intermittent intravenous or subcutaneous injection

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate- 11 months:** 0.15-0.25micrograms/kg/dose slowly over 3-5 minutes; repeated up to every 30-60 minutes
- **Child over 1 year:** 0.25–0.5micrograms/kg/dose, slowly over 3-5 minutes, repeated up to every 30-60 minutes
- **Adult** initial stat dose of 50–200micrograms, and subsequently 50micrograms, repeated up to every 30-60 minutes

### Notes:

- Synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.

### Licensing

- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.

### Therapeutics

- Evidence that it is less constipating than morphine has not been confirmed in more recent studies
- Buccal, intranasal and oral-transmucosal routes: onset of action 10-15 minutes and duration of action 1-2 hours depending on route and formulation. Therefore suitable for management of breakthrough pain but not ideal for titration of analgesic requirements in unstable pain.
- Some patients experience withdrawal symptoms when changed from oral morphine to transdermal fentanyl, despite adequate pain relief, due to the different mu receptor impact of the two drugs. If this occurs, small rescue doses of morphine can be used and weaned off slowly
- Intranasal administration has been reported for the treatment of dyspnoea in children
- Use adjusted body weight (Appendix 7) to calculate doses in obese children
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

### Contraindications, cautions

- The MHRA, CQC, and NHS England recommend NOT using transdermal fentanyl in opioid-naive patients due to numerous reports of respiratory depression.
- Greater risk of addiction, tolerance and drug seeking behaviour particularly when administered via buccal or intranasal routes, compared with longer acting opioids.

### Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine and phenobarbital.
- Fentanyl has been reported to reduce the metabolism of IV **midazolam**, reducing the clearance by 30% and extending the half-life by 50%



*Hepatic and renal impairment*

- Can be safely used in poor, deteriorating or absent renal function.
- Caution in hepatic impairment: Risk of accumulation. Consider dose reduction. May be safer than other opioids in hepatic failure and hepato-renal syndrome.

*Patient information*

- See Medicines for Children Leaflets “Fentanyl lozenges for pain” <https://www.medicinesforchildren.org.uk/medicines/fentanyl-lozenges-for-pain/> and “Fentanyl patches for pain” <https://www.medicinesforchildren.org.uk/medicines/fentanyl-patches-for-pain/>

*Administration*

*Intranasal*

- Intranasal onset of action and duration of action are shorter than oromucosal
- Not always practical and/or well tolerated in children despite favourable pharmacokinetics.
- Intranasal route has also been used for management of respiratory distress in paediatric palliative care.
- For doses less than 50micrograms, the injection solution can be administered by the intranasal route either drop-wise (may be unpleasant) or using a mucosal atomiser device.

*Lozenges, buccal / sublingual tablets*

- Fentanyl products for the treatment of breakthrough pain are not interchangeable. If patients are switched from another fentanyl containing product a new dose titration is required.
- Oral transmucosal fentanyl accumulates with repeated dosing
- Usefulness of lozenges and buccal / sublingual tablets in children is limited by the dose availability, no reliable conversion factor and requirement for individual dose titration.
- Oral transmucosal products are not suitable for opioid naive patients. Use only in patients receiving at least 60mg/24hours oral morphine equivalent for at least a week.
- The lozenge must be rotated in buccal pouch, not sucked. Older children will often choose to remove the lozenge before it is completely dissolved, giving them some much-valued control over their analgesia.

*Fentanyl transdermal patches*

- MHRA advises that *fentanyl* matrix patches must not be cut due to the risk of life threatening and potentially fatal opioid toxicity.
- Patches are not appropriate for initiation or titration phases of opioid management in palliative care due to large dose increments and time to achieve steady state.
- Initial evaluation of the analgesic effect cannot be made before the patch is worn for 24 hours.
- Patches should be changed every 72 hours and the site of application rotated. Some children who are rapid metabolisers need patch changes every 36-48 hours.
- After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore, after a dose increase, patients should wear the higher dose patch through two 72-hour applications before any further increase in dose level is made.
- After the patch is removed it may take 20 hours or more for serum fentanyl concentrations to decrease by 50% and significant blood concentrations persist for at least 24 hours.

Replacement opioid therapy should therefore be initiated at a low dose and increased gradually

- Remove patches before MRI scanning: risk of burns.
- Absorption may be increased in pyrexia, vigorous exercise or topical application of heat including warm baths or showers
- For rapidly escalating symptoms in the last few hours and days of life, continue transdermal fentanyl and an additional 1/10 to 1/6 total daily oral morphine equivalent as required. If more than 2 PRN-doses are required in 24 hours, continue transdermal fentanyl and add morphine CSCI at a dose equivalent to the total daily morphine dose administered over the previous 24 hours. Adjust the PRN-dose taking into account the total opioid dose (i.e. transdermal fentanyl + continuous subcutaneous morphine).

*Available as*

- Intranasal spray Instanyl® (50micrograms/spray, 100micrograms/spray and 200micrograms/ spray). PecFent® (100micrograms/ spray and 400micrograms/spray).
- Lozenge with oromucosal applicator Actiq®, Cynril® (200micrograms, 400micrograms, 600micrograms, 800micrograms, 1.2mg and 1.6mg).
- Buccal/sublingual tablets Abstral®(100 micrograms, 200 micrograms, 300 micrograms, 400 micrograms, 600 micrograms and 800micrograms) and buccal tablets Effentora(R) (100 micrograms, 200 micrograms, 400 micrograms, 600 micrograms and 800micrograms).
- Patches: various manufacturers (12micrograms/hour, 25micrograms/hour, 37.5micrograms/hour, 50micrograms/hour, 75micrograms/hour, 100micrograms/hour); Ionys® transdermal system (40micrograms/dose)
- Injection: 50micrograms per ml

*CD*

- Schedule 2 CD

## Fluconazole

### Use:

- Mucosal candidiasis infection (if nystatin not tolerated / effective), invasive candidal infections or prevention of fungal infections in immunocompromised patients

### Dose and route:

#### Mucosal candidal infection

By mouth or intravenous infusion:

- **Neonate up to 13 days:** 3-6mg/kg on first day then 3mg/kg every 72 hours
- **Neonate 14-28 days:** 3-6mg/kg on first day then 3mg/kg every 48 hours
- **Child 1 month-11 years:** 3-6mg/kg on first day then 3mg/kg, maximum 100mg daily
- **12 years and over:** 50mg/day. Increase to 100mg/day in severe infections.

Continue treatment for 7-14 days in oropharyngeal candidiasis and 14-30 days in other mucosal infections.

#### Invasive candidal infections and cryptococcal infections

By mouth or intravenous infusion:

- **Neonate up to 13 days:** 6-12mg/kg every 72 hours
- **Neonate 14-28 days:** 6-12mg/kg every 48 hours
- **Child 1 month and over:** 6-12mg/kg every 24 hours maximum 800mg daily

Continue treatment for a minimum of 8 weeks with duration of treatment determined by response.

#### Prevention of fungal infections in immunocompromised patients

By mouth or intravenous infusion

- **Neonate up to 13 days:** 3-12mg/kg every 72 hours
- **Neonate 14-28 days:** 3-12mg/kg every 48 hours
- **Child 1 month and over:** 3-12mg/kg every 24 hours, maximum 400mg daily

Commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range.

**Notes:**

- Fungistatic anti-fungal.

*Licensing*

- Licensed for treatment of fungal infections in all ages

*Therapeutics*

- Resistance may develop with long-term treatment. Use for 7-14 days in oropharyngeal candidiasis. Use for 14-30 days in other mucosal infections.

*Side effects*

- Most frequent (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

*Interactions*

- Potent inhibitor of cytochrome P450 enzyme CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Increases levels of drugs metabolised by these enzymes including alfentanil, buprenorphine, carbamazepine, dexamethasone, diazepam, diclofenac, fentanyl, midazolam and omeprazole. *This list is not exhaustive-see advice.*

*Administration*

- Intravenous infusion should be administered over 10–30 minutes at a rate not exceeding 5–10ml/minute
- Oral suspension may be administered via NG tube gastrostomy or jejunostomy. Bioavailability is unaffected by jejunal administration. Flush tube well after suspension is administered.

*Patient information*

- See Medicines for Children leaflet “Fluconazole for yeast and fungal infections”  
<https://www.medicinesforchildren.org.uk/medicines/fluconazole-for-yeast-and-fungal-infections/>

*Available as*

- Capsules (50mg, 150mg, 200mg); oral suspension (50mg/5ml, 200mg/5ml) and IV infusion (2mg/ml in 25ml, 50ml, 100ml).

## Fluoxetine

### Use:

- Major depression (seek specialist advice)

### Dose and route:

By mouth:

- **Child 5 years and over:** Initial dose 10mg once daily. May be increased after 1-2 weeks if necessary to a maximum of 20mg once daily.

### Notes:

- Selective serotonin reuptake inhibitor (SSRI).

### Licensing

- Licensed for use in children from 8 years of age.

### Therapeutics

- Onset of benefit 3-4 weeks in depression
- Consider long half-life when adjusting dosage.
- Do not discontinue abruptly.
- May be beneficial in neuropathic pain and intractable cough.
- Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

### Contraindications, cautions

- Caution in children: seek specialist advice. Caution in cardiac disease and poorly controlled epilepsy.

### Side effects

- Increased risk of bleeding due to antiplatelet function.
- Increased risk of anxiety for first 2 weeks.
- 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.
- Headache, nausea, insomnia, fatigue and diarrhoea.
- Movement disorders
- Increased risk of seizures

### Interactions

- Inhibits cytochrome P450 enzymes CYP2C19 and CYP2D6. Increases levels of drugs metabolised by these enzymes including amitriptyline, carbamazepine, diazepam and erythromycin. *This list is not exhaustive –seek advice.*
- Must not be used in combination with a MAOI: risk of serotonin syndrome

*Administration*

- Oral liquid may be administered via NG tube or gastrostomy. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children leaflet “Fluoxetine for depression, obsessive compulsive disorder and bulimia nervosa”  
<https://www.medicinesforchildren.org.uk/medicines/fluoxetine-for-obsessive-compulsive-disorder-ocd-depression-and-bulimia-nervosa/>

*Available as*

- Capsules (10mg, 20mg, 30mg, 40mg, 60mg) dispersible tablets (20mg) and oral liquid (20mg/5ml).

## Gabapentin

### Use:

- Adjuvant in neuropathic pain
- CNS irritability
- Visceral hyperalgesia
- Management of abnormal tone and movement disorders
- Uraemic Itch
- Intractable hiccup
- Epilepsy
- Restless legs syndrome in chronic kidney disease

#### Important safety information

#### **MHRA/CHM advice: Gabapentin (Neurontin®): risk of severe respiratory depression (October 2017)**

Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, and concomitant use of central nervous system (CNS) depressants, might be at higher risk of experiencing severe respiratory depression, and dose adjustments may be necessary in these patients.

### Dose and route:

#### **Neuropathic pain, all indications other than epilepsy**

#### By mouth:

Consider introducing gabapentin more slowly in debilitated patients, or when administered with other CNS depressants

- **Neonate-23 months:** 5mg/kg/dose. Administer once daily on day 1, administer twice daily on day 2 then three times daily from day 3 onwards.

Increase further, if necessary, in increments of 5-10mg/kg in 3 divided doses, every 3–7 days. Maximum 10mg/kg/dose

- **Child 2-11 years:** 5-10mg/kg/dose, maximum single dose 300mg. Administer once daily on day 1, administer twice daily on day 2 then three times daily from day 3 onwards.

Increase further, if necessary, in increments of 5–10mg/kg in 3 divided doses, every 3–7 days. Maximum 20mg/kg/dose. Maximum single dose 600mg

- **12 years and over:** Initially 300mg once daily on day 1, then 300mg twice daily on day 2, then 300mg three times daily from day 3 onwards.

Increase further, if necessary in steps of 300mg every 3-7 days given in 3 divided doses daily. Maximum 3600mg total daily dose

### **Gabapentin to pregabalin switch for neuropathic pain**

See Appendix 5

### **Epilepsy**

Consult BNFC or local neurology protocols. Gabapentin is now rarely used as a primary treatment for epilepsy.

### **Notes:**

#### *Licensing*

- Licensed as an adjunct for the treatment of focal seizures in patients over 6 years and as a monotherapy for the treatment of focal seizures in patients over 12 years. Maximum licensed dose 50mg/kg/day for under 12 years. Not licensed for neuropathic pain in children.

#### *Therapeutics*

- Animal evidence suggests anti-seizure and analgesic activity of gabapentin is mediated via binding to the alpha-2 subunit of voltage gated calcium channels in the CNS with subsequent inhibition of excitatory neurotransmitter release and/or inhibition of descending inhibitory pain pathways.
- Doses can be titrated more slowly with increases every 1–2 weeks in debilitated patients or co-administration with other CNS depressants
- Higher doses (up to 20mg/kg TDS) have been used in the management of severe dystonia. These higher doses are reached by slow upwards titration guided by the child's response.
- No consensus on dose for neuropathic pain. Doses shown are based on doses for partial seizures and authors' experience.
- Adult evidence for use in pruritus in anaemia, anxiety, hot flushes, sweating, refractory hiccups, restless legs syndrome and refractory cough.
- Risk of dependence and diversion for substance abuse

#### *Side effects*

- Very common (>1 in 10) side effects: somnolence, dizziness, ataxia, viral infection, fatigue, fever.

#### *Pharmacokinetics*

- Oral bioavailability of approximately 60%. However gabapentin absorption is saturable, leading to a non-linear pharmacokinetic profile and decrease in bioavailability with increasing gabapentin dose. Bioavailability also varies with patient population. Careful titration of dose is required.
- Peak plasma concentrations occur 2-3 hours after oral dosing.
- Bioavailability is not affected by food. Co-administration with antacids containing aluminium and magnesium can reduce bioavailability by up to 24%. Manufacturers recommend giving gabapentin two hours after antacids.



*Hepatic impairment, renal impairment*

- Gabapentin is solely excreted unchanged by the kidneys. Reduce dose in renal impairment (consult manufacturer's literature).

*Interactions*

- Morphine may increase gabapentin concentrations. Consider reducing the dose of gabapentin or opioids as clinically appropriate.

*Administration*

- Capsules can be opened and suspended in water or fruit juice (to hide the bitter taste) as an alternative to oral solution.
- Absorbed in proximal small bowel. The oral solution or the capsule contents (dispersed in water) can be given via a NG tube or gastrostomy. Flush tube well after administration.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children leaflet "Gabapentin for neuropathic pain": <https://www.medicinesforchildren.org.uk/gabapentin-for-neuropathic-pain> and "Gabapentin for preventing seizures" <https://www.medicinesforchildren.org.uk/gabapentin-for-preventing-seizures>

*Available as*

- Capsules (100mg, 300mg, 400mg); tablets (600mg, 800mg), oral solution 250mg/5 ml (Neurontin, United States import). Oral solution 50mg/ml now available as licensed preparation in UK. May contain high amount of propylene glycol as an excipient

*CD*

- Schedule 3 CD but exempt from safe custody requirements.

## Gaviscon®

### Use:

- Gastro-oesophageal reflux, dyspepsia and heartburn.

### Dose and route:

By mouth:

Gaviscon Infant® (sodium alginate with magnesium alginate) sachets:

- **Neonate-2 years, body-weight less than 4.5kg:** 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 4.5kg and over:** 2 doses (1 dual sachet) when required mixed with feeds or with water for breast fed babies or older infants, maximum 12 doses (6 dual sachets) in 24 hours

Gaviscon Liquid and Tablets (Sodium alginate, calcium carbonate, sodium bicarbonate)

- **Child 2-11 years:** 1 tablet or 5-10ml liquid after meals and at bedtime
- **12 years and over:** 1-2 tablets or 10-20ml liquid after meals and at bedtime

Gaviscon Advance (Sodium alginate, potassium bicarbonate)

- **Child 2-11 years:** 1 tablet or 2.5-5ml suspension after meals and at bedtime (under medical advice only)
- **12 years and over:** 1-2 tablets or 5-10ml suspension after meals and at bedtime

### Notes:

#### *Licensing*

- Gaviscon Infant Sachets licensed for infants and young children up to 2 years of age, but use under 1 year only under medical supervision. Gaviscon liquid and tablets are licensed for use from 2 years of age but age 2-6 years only on medical advice. Gaviscon Advance suspension and tablets are licensed for use from 12 years of age; use under 12 years on medical advice only.

#### *Contraindications, cautions*

- Gaviscon Infant should not to be used with feed thickeners, nor in patients with excessive fluid losses (e.g. fever, diarrhoea, vomiting).

- Gaviscon Liquid contains 3.1mmol sodium per 5ml; Gaviscon tablets contain 2.65mmol sodium and also contain aspartame. Gaviscon Infant Sachets contain 0.92mmol sodium per dose (half dual sachet).

*Administration*

- Can be administered via nasogastric tube or gastrostomy. Calcium may bind to any phosphate in an enteral feed causing tube blockage. A prolonged break in feeding is not required, but the tube should be adequately flushed to ensure that the calcium supplement does not come into contact with the feed. Not appropriate for administration via jejunostomy.

*Patient information*

- See Medicines for Children leaflet “Gaviscon for gastro-oesophageal reflux disease”:  
<https://www.medicinesforchildren.org.uk/medicines/gaviscon-for-gastro-oesophageal-reflux-disease/>

*Available as*

- Gaviscon liquid and tablets; Gaviscon Advance suspension and tablets; Infant Sachets (comes as dual sachets, each half of dual sachet is considered one dose).

## Glycerol (glycerin)

### Use:

- Constipation

### Dose and routes

By rectum:

- **Neonate over 34 weeks corrected gestational age:** Tip of a glycerol suppository (slice a small chip off a 1g suppository with a blade)
- **Child 1 month-11 months:** 1g infant suppository as required
- **Child 1-11 years:** 2g child suppository as required
- **Child 12-17 years:** 4g adult suppository as required

### Notes:

- Hygroscopic and lubricant actions. May also be a rectal stimulant.

### *Licensing*

- 1g suppositories licensed for use in infants up to 1 year of age, 2g suppositories licensed for use in children aged 1-11 years, 4g suppositories licensed for use from 12 years of age.

### *Side effects*

- Associated with necrotising enterocolitis in babies less than 34 weeks gestation.

### *Pharmacokinetics*

- Response usually in 20 minutes to 3 hours.

### *Administration*

- Moisten with water before insertion.

### *Patient information*

- See Medicines for Children leaflet “Glycerin (glycerol) suppositories for constipation” <https://www.medicinesforchildren.org.uk/medicines/glycerin-glycerol-suppositories-for-constipation/>

### *Available as*

- Suppositories (1g, 2g, and 4g)

## Glycopyrronium bromide

### Use:

- Control of upper airways secretions
- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation and drooling
- Bowel colic pain
- Paraneoplastic sweating or pyrexia

### Dose and route:

By mouth:

Using **Sialanar**<sup>®</sup> glycopyrronium *bromide* 400micrograms/ml oral solution

- **Child 1 month and over:** 16micrograms/kg 3 times daily, increased in steps of 16micrograms/kg 3 times daily, every 7 days, adjusted according to response

Maximum 80micrograms/kg 3 times daily, maximum 2.4mg/dose

Using **generic** 1mg/5ml oral solution

- **Child 1 month and over:** 20micrograms/kg 3 times daily, increased in steps of 20micrograms/kg 3 times daily, every 5-7 days, adjusted according to response

Maximum 100micrograms/kg 3 times daily, maximum 3mg/dose

By subcutaneous or intravenous injection:

- **Child 1 month-11 years:** Initial dose of 4micrograms/kg 3-4 times daily. The dose may be increased as necessary to 10micrograms/kg 3-4 times daily,

Maximum 200micrograms/dose 4 times daily

- **12 years and over:** 200micrograms 3-4 times daily

By continuous subcutaneous or intravenous infusion:

- **Child 1 month-11 years:** Initial dose of 12micrograms/kg/24hours, increased as necessary to 40micrograms/kg/24hours, maximum 1.2mg/24hours

- **12 years and over:** 600micrograms/24hours, increased as necessary to 1.2mg/24hours.

### Notes:

- Antimuscarinic

*Licensing*

- Licensed oral solutions (Sialanar®, generic) are licensed for use in children from 3 years of age with a chronic neurological disorder, for chronic pathological drooling. Not licensed for use in children for control of upper airways secretion and hypersalivation.

#### *Therapeutics*

- Excessive secretions can distress the child, but more often distress those around him/her.
- Treatment is more effective if started before secretions become too much of a problem.
- More frequent subcutaneous administration, up to hourly, is occasionally required in adults.
- Adult evidence for use in smooth muscle spasm (e.g. intestine, bladder), inoperable intestinal obstruction, hyperhidrosis, para-neoplastic pyrexia and sweating.
- Injection solution has also been given sublingually in adults using same doses as subcutaneous or intravenous bolus

#### *Side effects*

- Antimuscarinic side effects including constipation, urinary retention, tachycardia, blurred vision

#### *Pharmacokinetics*

- 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.

#### *Renal impairment*

- Risk of accumulation: reduce dose or avoid

#### *Administration*

- Administration by CSCI: good compatibility data available for mixing with other commonly used palliative agents.
- Co-administration with food results in a marked decrease in systemic medicinal product exposure. Dosing should be at least one hour before or at least two hours after meals, or at consistent times with respect to food intake. High fat food should be avoided. Where the child's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake.
- Tablets may be dispersed in water immediately prior to administration via feeding tubes, or use the oral solution. Flush tube immediately with 10-20 ml water. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

#### *Available as*

- Tablets (1mg, 2mg), oral solution 200micrograms/ml as glycopyrronium bromide (various) and 400micrograms/ml as glycopyrronium *bromide* (Sialanar®), injection (200micrograms/ml 1ml and 3ml ampoules).
- Glycopyrronium bromide tablets and oral solutions are not interchangeable on a microgram-for-microgram basis due to differences in bioavailability. Sialanar® oral solution has approximately 25% higher bioavailability and therefore equivalent doses will be lower than for tablets and generic oral solutions. The prescriber should state the

specific branded or generic oral preparation to be used; care should be taken if switching between oral preparations and dosing adjusted accordingly.



## Haloperidol

### Use:

- Nausea and vomiting where cause is metabolic, or in difficult to manage cases such as end stage renal failure.
- Delirium
- Agitation in the last hours and days of life.
- Intractable hiccups.
- Psychosis (including steroid-induced), hallucinations.
- Persistent severe aggression in autism or pervasive developmental disorders (under specialist supervision).

### Dose and route:

#### Nausea and vomiting, delirium, agitation at end of life:

By mouth

- **Child 1 month-11 years:** 20micrograms/kg/dose, maximum 1mg, once daily at night, increased as necessary to a maximum of 180micrograms/kg/dose, maximum 10mg. Can also be given in 2 or 3 divided doses
- **12 years and over:** 1mg once daily at night, increased as necessary to 10mg at night. Can also be given in 2 or 3 divided doses

By continuous intravenous or subcutaneous infusion

- **Child 1 month-11 years:** 20micrograms/kg/24hours (maximum 1mg/24hours), increased as necessary to a maximum of 90micrograms/kg/24hours
- **12 years and over:** Initial dose of 1mg/24hours. The dose may be increased as necessary to a maximum of 5mg/24hours.

#### Intractable hiccups

By mouth

- **Child 1 month-11 years:** 20micrograms/kg/dose (maximum 1mg) 3 times daily, increased as necessary to a maximum of 60micrograms/kg/dose (maximum 3mg) 3 times daily. Once hiccups are controlled reduce to stop or to lowest possible maintenance dose.

- **12 years and over:** 1mg 3 times daily, increased as necessary to maximum 3mg 3 times daily. Reduce to stop or to lowest possible maintenance dose once hiccups are controlled.

**Notes:**

- D2 receptor antagonist and typical antipsychotic.

### *Licensing*

- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for intramuscular administration in adults

### *Therapeutics*

- Higher doses may be used under specialist advice. If nausea and vomiting are not controlled on maximal doses via continuous infusion, review cause(s) and consider changing to levomepromazine
- For dosage in psychosis discuss with child psychiatrist.
- Dosages for agitation and confusion are often higher.
- Adult dosages can exceed 15mg/24hours in severe agitation
- Oral solution (2mg/ml) has also been given sublingually using same doses as oral or rectal routes

### *Contraindications, cautions*

- Contraindicated in congenital long QT syndrome; history of Torsade de Pointes; history of ventricular arrhythmia; QTc-interval prolongation
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those at risk of, prolonged QT- interval e.g. those with cardiac abnormalities, hypothyroidism, electrolyte imbalance or taking other drugs known to prolong the QT-interval

### *Side effects*

- Associated with prolonged QT-interval and Torsades de Pointes, particularly if given intravenously or at higher than recommended doses.
- Side effects vary between age groups, with behavioural problems being common in children.
- Extrapyramidal side effects, neuroleptic malignant syndrome

### *Pharmacokinetics*

- Oral bioavailability approximately 50%. Consider reducing dose when converting from oral to intravenous or subcutaneous routes

### *Interactions*

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including erythromycin and fluconazole. Levels may be reduced by drugs that induce this enzyme.

### *Administration*

- Oral solutions may be administered via feeding tubes without further dilution. Flush tube well following administration. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

### *Available as*

- Tablets (500 micrograms, 1.5mg, 5mg, 10mg), capsules (500 micrograms), oral liquid (200 micrograms/ml, 1mg/ml, 2mg/ml), and injection (5mg/ml).

## Hydromorphone

### Use:

- Alternative opioid analgesic for severe pain especially if intolerant to other strong opioids.

Important safety information

#### For all opioids

#### MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The **APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### Pain in patients already receiving regular strong opioids

By mouth using immediate release preparations

Convert using oral morphine equivalent (OME) from previous opioid analgesia, see Appendix 1

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Hydromorphone oral	5:1	Divide 24hour morphine dose by 5	Morphine oral 10mg ÷ 5 = hydromorphone oral 2mg

By mouth using modified release preparations

- Calculate the total daily dose (regular + PRN) of oral hydromorphone administered over the previous 24 hours once the patient is established on regular hydromorphone for 2-3 days

*12-hourly preparations:* Divide the total daily dose of oral hydromorphone by two and administer every 12 hours

Consider reducing the dose of hydromorphone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Ensure continued access to immediate release hydromorphone as required for breakthrough pain, see below.

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of opioid administered over the previous 24 hours

Convert to the equivalent dose of CSCI hydromorphone using the table

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Hydromorphone CSCI or CIVI	10:1	Divide 24hour morphine dose by 10	Morphine oral 30mg ÷ 10 = hydromorphone CSCI 3mg
Morphine CSCI or CIVI	Hydromorphone CSCI or CIVI	5:1	Divide 24hour morphine dose by 5	Morphine CSCI 25mg ÷ 5 = hydromorphone CSCI 5mg
Hydromorphone Oral	Hydromorphone CSCI or CIVI	2:1	Divide 24hour hydromorphone dose by 2	Hydromorphone 10mg oral ÷ 2 = CSCI 5mg hydromorphone

Consider reducing the dose of hydromorphone by 25-50% when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

Ensure continued access to immediate release hydromorphone as required for breakthrough pain see below

**Breakthrough Pain in patients already receiving regular strong opioids**

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10 to 1/6 of total daily hydromorphone dose every 1-4 hours as required.
- If the route for breakthrough analgesia is different to the route for background analgesia (e.g. CSCI with oral breakthrough) convert the breakthrough dose as above to the required route

Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

### **Pain in opioid naïve patients**

By mouth:

Opioid naïve patients: the maximum dose stated applies to starting dose only

- **Child 1 year and above:** 25micrograms/kg per dose maximum 2mg per dose every 4 hours increasing as required.
- **12 years and above:** 1.3mg every 4 hours increasing as required

By subcutaneous or slow intravenous injection:

- **Child 1 year and above:** 12micrograms/kg per dose every 4 hours, increasing as required

### **Notes:**

- Analogue of morphine with similar pharmacokinetic and pharmacodynamics

#### *Licensing*

- Licensed for the relief of severe pain in cancer in adults and adolescents aged over 12 years.

#### *Side effects*

- Usual opioid side effects

#### *Pharmacokinetics*

- 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.
- Main metabolite is hydromorphone-3-glucuronide (H3G). H3G has no analgesic activity but, like morphine-3-glucuronide (see morphine), it is a CNS neuro-excitant.
- All metabolites are renally excreted and can accumulate in renal impairment.
- More soluble than morphine, and available as a high-concentration injection (50mg/ml). Alternative to diamorphine when high doses need to be administered by CSCI
- Plasma half- life 2.5 hours early phase, prolonged late phase: duration of action 4-5 hours.

- Equianalgesic ratios vary more than for other opioids: possibly due to inter-individual variation in metabolism or bioavailability.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

*Hepatic impairment, renal impairment*

- Caution in hepatic impairment, use at reduced doses. Avoid in severe hepatic impairment
- Caution in renal impairment, use at reduced starting doses.

*Administration*

- For CSCI dilute with water for injection, sodium chloride 0.9% or glucose 5%.
- Modified release capsules are given 12-hourly.
- Capsules (both types) can be opened and contents sprinkled on soft food. Do not administer via feeding tubes due to risk of blockage

*Available as*

- Capsules (1.3mg, 2.6mg) and modified release capsules (2mg, 4mg, 8mg, 16mg, 24mg). Injection (2mg/ml, 10mg/ml, 20mg/ml and 50mg/ml). Oral solution available as a manufacturer's special.

*CD*

- CD schedule 2

## Hyoscine butylbromide (Buscopan)

### Use:

- Adjuvant where pain is caused by smooth muscle spasm of the gastrointestinal or genitourinary tract
- Antisecretory effect in bowel obstruction
- Management of secretions, especially where drug crossing the blood brain barrier is an issue
- Management of noisy breathing at the end of life (may be more effective if started early)

### Dose and route:

#### Adjuvant in smooth muscle spasm of the gastrointestinal tract

By mouth

- **Child 1 month-1 year:** 300-500micrograms/kg 3–4 times daily, maximum 5mg per dose
- **Child 2 -4 years:** 5mg 3–4 times daily
- **5- 11 years:** 10mg 3–4 times daily
- **12 years and over:** 10–20mg 3–4 times daily

By subcutaneous bolus injection, intravenous injection or intramuscular injection

- **Child 1 month- 4 years:** 300–500micrograms/kg 3-4 times daily, maximum 5mg per dose
- **5-11 years:** 5–10mg 3–4 times daily
- **12 years and over:** 10–20mg 3–4 times daily

By continuous subcutaneous infusion:

- **Child 1 month- 4 years:** 1.5mg/kg/24hours (max 15mg/24hours)
- **Child 5-11 years:** 30mg/24hours
- **12 years and over:** Up to 60-80mg/24hours

Higher doses may be needed; doses used in adults range from 20-120mg/24hours.  
Maximum dose 300mg/24hours.

#### Adjuvant in smooth muscle spasm of gastrointestinal and urinary tract, antisecretory effect in bowel obstruction, management of respiratory secretions

By subcutaneous bolus injection, intravenous injection or intramuscular injection

- **Child 1 month-4 years:** 300–500micrograms/kg 3-4 times daily, maximum 5mg per dose



- **Child 5-11 years:** 5–10mg 3–4 times daily
- **12 years and over:** 10– 20mg 3–4 times daily

By continuous subcutaneous infusion:

- **Child 1 month- 4 years:** 1.5mg/kg/24hours (max 15mg/24hours)
- **Child 5-11 years:** 30mg/24hours
- **12 years and over:** Up to 60-80mg/24hours

Higher doses may be needed; doses used in adults range from 20-120mg/24hours.  
Maximum dose 300mg/24hours.

### **Notes:**

- Antimuscarinic and has smooth muscle relaxant and antisecretory properties

#### *Licensing*

- Tablets are not licensed for use in children <6 years old. Injection is not licensed for use in children.

#### *Therapeutics*

- Does not cross blood brain barrier (unlike hyoscine hydrobromide), hence no central antiemetic effect and doesn't cause drowsiness.
- More likely to be effective in death rattle if used prophylactically

#### *Contraindications, cautions*

- Contraindicated in patients with tachycardia. Caution in cardiac disease. The MHRA recommends that patients with cardiac disease are monitored and that resuscitation equipment and trained personnel are readily available: this may not be appropriate in end of life care
- Increased risk of cardiac arrhythmia and anaphylaxis in patients with underlying cardiac disease.
- Likely to exacerbate gastro-oesophageal reflux

#### *Side effects*

- Anti-muscarinic side effects including constipation, urinary retention, tachycardia, blurred vision.

#### *Pharmacokinetics*

- Onset of action less than 10 min for SC/IV; 1-2 hours orally. Time to peak plasma concentration 15 min-2 hours orally. Plasma half-life 1-5 hours. Duration of action less than 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 oral administration probably relates to a local contact effect on the GI mucosa.

#### *Administration*

- Injection solution may be given orally or via an enteral feeding tube. Administration via jejunostomy bypasses local effects on GI tract and is not recommended. Injection solution can be stored for 24 hours in the refrigerator after opening.
- Slow IV injection over 1 minute, diluted with glucose 5% or sodium chloride 0.9%.

#### *Available as*

- Tablets (10mg) and injection (20mg/ml).

## Hyoscine hydrobromide

### Use:

- Control of upper airways secretions
- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation and drooling
- Bowel colic pain
- Paraneoplastic sweating or pyrexia

### Dose and routes

By mouth or buccal route:

- **Child 1 month- 11 years:** 10micrograms/kg, maximum 600micrograms, 4 times daily
- **12 years and over:** 300micrograms 4 times daily, increased gradually to a maximum of 600micrograms 4 times daily if required

By transdermal route:

- **Neonate over 32 weeks corrected gestational age, child up to 2 years:**  
250micrograms  
(1/4 x 1mg/72hour patch) every 72 hours
- **Child 3-9 years:** 500micrograms (1/2 x 1mg/72hours patch) every 72 hours
- **10 years and over:** 1mg (1 x 1mg/72hours patch) every 72 hours

By subcutaneous or intravenous injection or infusion:

- **Child 1 month-17 years:**  
10micrograms/kg, maximum 600micrograms, every 4–8 hours  
OR 40-60micrograms/kg/24hours via CSCI/IV infusion.

Maximum suggested dose is 2.4mg in 24 hours: higher doses may be used by specialist units.

### Notes:

- Antimuscarinic with smooth muscle relaxant and antisecretory properties

#### *Licensing*

- Not licensed for use in children for control of upper airways secretion or hypersalivation.

#### *Therapeutics*

- Higher doses often used under specialist advice.
- Second line, after glycopyrronium bromide, for treatment of hypersalivation in cerebral palsy

*Contraindications, cautions*

- MHRA (July 2023): Hyoscine hydrobromide patches (Scopoderm 1.5mg Patch or Scopoderm TTS Patch): risk of anticholinergic side effects, including hyperthermia particularly when used outside the product licence
- Transdermal patches contain metal in the backing and must be removed before MRI scanning to avoid burns.

*Side effects*

- Side effects: common or very common: confusion; constipation; dizziness; drowsiness; dry mouth; dyspepsia; flushing; headache; nausea; palpitations; skin reactions; tachycardia; urinary disorders; vision disorders; vomiting. Frequency unknown: neuroleptic malignant syndrome

*Administration*

- Apply patch to hairless area of skin behind ear.
- The patch can cause alteration of the pupil size on the side it is placed.
- Manufacturers of Scopoderm TTS patch have confirmed that it is safe to cut patches although this is outside the scope of product licence
- Injection solution may be administered orally and via feeding tubes. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Tablets (150micrograms, 300micrograms), patches (releasing 1mg/72 hours), and injection (400micrograms/ml, 600micrograms/ml).
- An oral solution is available via a 'specials' manufacturer.

## Ibuprofen

### Use:

- Non-steroidal analgesic
- Anti-pyretic
- Adjuvant for musculoskeletal pain.

### Dose and routes

#### Pain and inflammation

By mouth using immediate release preparations

- **Neonate:** 5mg/kg/dose every 12 hours
- **Child 1-2 months:** 5mg/kg 3–4 times daily preferably after food
- **Child 3-5 months:** 50mg 3 times daily preferably after food; in severe conditions up to 30mg/kg daily in 3–4 divided doses
- **Child 6-11 months:** 50mg 3–4 times daily preferably after food; in severe conditions up to 30mg/kg daily in 3–4 divided doses
- **Child 1-3 years:** 100mg 3 times daily preferably after food. In severe conditions up to 30mg/kg daily in 3–4 divided doses
- **Child 4-6 years:** 150mg 3 times daily, preferably after food. In severe conditions, up to 30mg/kg daily in 3–4 divided doses
- **Child 7-9 years:** 200mg 3 times daily, preferably after food. In severe conditions, up to 30mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4g
- **Child 10-11 years:** 300mg 3 times daily, preferably after food. In severe conditions, up to 30mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4g
- **12 years and over:** 300-400mg 3-4 times daily preferably after food. In severe conditions the dose may be increased to a maximum daily dose 2.4g

By mouth using modified release preparations

- **12 years and over:** 1.6g once daily, dose preferably taken in the early evening, increased to 2.4g daily in 2 divided doses if necessary.

#### Pain and inflammation in rheumatic diseases, including idiopathic juvenile arthritis:

By mouth using immediate release preparations

- **Child aged 3 months and over:** 30–40mg/kg daily in 3–6 divided doses preferably after food. Increased, if necessary to a maximum of 60mg/kg/day. Maximum daily dose 2.4g

**Notes:**

- Non-opioid analgesic, NSAID and non-selective COX inhibitor

*Licensing:*

- Orphan drug licence for closure of ductus arteriosus in preterm neonate. Not licensed for use in children less than 3 months of age or body-weight less than 5kg, except for up to two doses for post immunisation pyrexia. (50mg/dose given a minimum of 6 hours apart). Topical preparations and granules are not licensed for use in children.

*Therapeutics*

- Combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side effects than other NSAIDs but its anti-inflammatory properties are weaker.
- Alternating or combining with paracetamol may give better antipyretic effect than monotherapy but benefits in terms of analgesia are unclear.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

*Contraindications, cautions*

- Caution in patients with or at risk of thrombocytopenia: may impair platelet function.
- May mask fever and other signs of inflammation
- Will cause closure of ductus arteriosus; contraindicated in duct-dependent congenital heart disease
- Caution in cardiac, hepatic or renal impairment and those with asthma. Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

*Side effects*

- May be associated with an increased risk of thrombotic events (e.g. myocardial infarction, thrombotic stroke) in children.
- All NSAIDs are associated with gastro-intestinal toxicity however lowest risk is likely to be with ibuprofen. Consider prescription of a proton pump inhibitor with prolonged use.

*Hepatic impairment, renal impairment:*

- Avoid or use with caution in severe renal failure.

*Administration*

- For administration via an enteral feeding tube, use a liquid preparation; dilute with an equal volume of water immediately prior to administration where possible. No specific information for jejunal administration. Administer as above and monitor for any signs of loss of efficacy or increased side effects.
- Can be used topically particularly for sprains, strains and arthritis.

*Patient information*

- Patient information: See Medicines for Children leaflet: “Ibuprofen for pain and inflammation” <https://www.medicinesforchildren.org.uk/medicines/ibuprofen-for-pain-and-inflammation/>

*Available as*

- Tablets (200mg, 400mg, 600mg), modified release tablet (800mg), orodispersible tablets (200mg), chewable capsules (100mg), capsules (200mg, 400mg), modified release capsules (200mg, 300mg), oral syrup (100mg/5ml), granules (600mg/sachet), topical foam (50mg per 1g) creams and gels (5%).

## Ipratropium Bromide

### Use:

- Wheeze or breathlessness caused by bronchospasm
- Rhinorrhoea associated with allergic and non-allergic rhinitis
- Localised management of sialorrhoea (with fewer systemic side effects)

### Dose and routes:

#### Wheeze or breathlessness caused by bronchospasm

By inhalation of nebulised solution

- **Child 1 month-5 years:** 125-250micrograms as required maximum 1mg daily
- **Child 6-11 years:** 250micrograms as required maximum 1mg daily
- **12 years and over:** 500micrograms as required maximum 2mg daily

By aerosol inhalation

Use via large volume spacer (and a close-fitting face mask in children under 3 years).

- **Child 1 month-5 years:** 20micrograms 3 times daily
- **Child 6-11 years:** 20-40micrograms 3 times daily
- **12 years and over:** 20-40micrograms 3-4 times daily

#### Rhinorrhoea associated with allergic and non-allergic rhinitis

By intranasal administration

- **12 years and over:** 2 sprays 2–3 times daily, dose to be sprayed into each nostril.

### Notes

#### *Licensing*

- Not licensed for severe or life-threatening acute asthma. Inhalvent® not licensed for use in children under 6 years. Not licensed for rhinorrhoea

#### *Therapeutics*

- In severe acute asthma, dose can be repeated every 20-30 minutes in first two hours, then every 4-6 hours as necessary (unlicensed).
- No evidence of efficacy in infection-related bronchospasm in infants

- Use in management of sialorrhoea in children not well established

*Side effects*

- Anti-muscarinic side effects occur with systemic absorption, including constipation, urinary retention, tachycardia, blurred vision.

*Pharmacokinetics*

- Maximum effects 30-60 minutes after use. Duration of action 3-6 hours.  
Bronchodilation can usually be maintained with treatment 3 times daily.

*Administration*

- 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.

*Available as*

- Nebuliser solution (250micrograms in 1 ml, 500micrograms in 2 ml), aerosol inhaler (20micrograms per metered dose), nasal spray 21micrograms per metered dose.



## Ketamine

### Use:

- Neuropathic pain and hyperalgesia
- Pain failing to respond to usual treatments, including opioids, non-opioids and adjuvant analgesics
- Adjuvant to strong opioids
- Severe visceral pain
- Ischaemic pain
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance.
- Emerging use in refractory status epilepticus.

### Dose and routes

#### Pain including NMDA wind-up pain

By mouth, or buccal route

- **Neonate (over 37 weeks corrected gestational age)- child 11 years:** Starting dose 100micrograms/kg, as required or regularly 6–8 hourly. Increase in increments of 100micrograms/kg up to 400micrograms/kg as required.
- **12 years and over:** 5-10mg as required or regularly 6–8 hourly; increase in steps of 5-10mg up to 50mg/dose as required.

Doses up to 200mg or 3mg/kg 4 times daily reported in adults

By continuous subcutaneous or intravenous infusion:

- **Child 1 month and over:** Starting dose 500micrograms/kg/24hours to 1mg/kg/24hours. Increase according to response; usual maximum 12mg/kg/24hours or 500mg/24hours

Doses up to 60mg/kg/24hours have been reported, including in refractory status epilepticus.

#### By intravenous administration for anaesthesia

Seek specialist advice

### Notes:

- Dissociative anaesthetic which has analgesic properties in sub-anaesthetic doses.
- Racemic mixture of the S(+) and R(–) stereoisomers of ketamine. The most potent NMDA-receptor–channel blocker available for clinical use

*Licensing*

- Not licensed for use in children with neuropathic pain.

#### *Therapeutics*

- Potential secondary benefits in adolescents with depressive symptoms.
- Continuous intravenous infusion of ketamine appears effective in refractory status epilepticus, but its place in clinical practice remains to be determined.
- Higher starting doses may be used, particularly by infusion, in anaesthesia and acute postoperative pain
- Generally administered orally or subcutaneously in palliative care. Can also be administered via intramuscular, intravenous, buccal, intranasal, spinal and rectal routes.
- Has also been administered topically for mucositis and painful wounds although RCT evidence is lacking.
- Buccal dose is effective but bitter taste. May result in increased drowsiness and slightly lower efficacy due to lack of first pass metabolism
- S-ketamine is licensed in many countries: use 50% of doses quoted above
- Short courses are preferred to long term use due to cumulative adverse effects including cognitive impairment and also renal tract damage.
- Once analgesia has been obtained, an attempt should be made to withdraw ketamine over 2–3 weeks. The benefit from a short course can last for weeks or even months, and the course can be repeated if necessary.
- Alternatively ketamine can be given as a short “burst” increasing doses stepwise rapidly over a period of 3-4 days until a therapeutic effect is achieved or side effects prevent further dose escalation and then decreasing in a similar stepwise fashion to stop after 7-10 days
- Some practitioners routinely reduce the background opioid dose by 25–50% when starting parenteral ketamine.
- Sudden discontinuation may precipitate hyperalgesia or allodynia: discontinue gradually over 2-3 weeks after prolonged use.

#### *Side effects*

- Neuropsychiatric side effects including agitation, hallucinations, anxiety and dysphoria, diplopia, nystagmus and sleep disturbance. Animal studies indicate that ketamine can induce neuronal cell death in the immature brain. Emergent phenomena occur to a lesser extent with the sub-anaesthetic analgesic doses given in palliative care, and generally can be controlled by concurrent administration of a benzodiazepine (e.g. diazepam, midazolam) or haloperidol.
- Gastrointestinal side effects include vomiting, abdominal pain, gastrointestinal bleeding, abnormal liver function tests and biliary duct dilatation
- Urological side effects include urinary frequency, urgency, dysuria, and haematuria

#### *Pharmacokinetics*

- Wide variation in clearance, mostly explained by genetic polymorphism in the activity of CYP2B6 together with increasing age
- Oral bioavailability is approximately 20% but ketamine is potentiated by first pass metabolism. In practical terms it is therefore reasonable to use a 1 to 1 ratio for conversion between oral and subcutaneous or intravenous routes.
- Onset of action 5 min IM; 15-30 min SC; 30 min PO. Duration of action 30 min–2h IM; 4-6h PO, sometimes longer. Bio-availability 93% IM; 45% nasal; 30% SL; 30% PR; 20% PO.

#### *Hepatic and renal impairment*

- Causes hepatic enzyme induction and enhances its own metabolism. Caution in severe hepatic impairment, consider dose reduction.

#### *Interactions*

- Diazepam can increase the half-life and prolong the effects of ketamine.

*Administration*

- Buccal doses should be prepared in a maximum volume of 2 ml. The bitter taste may make this route unpalatable. Special preparations for buccal use are available in UK.
- Dilute in 0.9% sodium chloride for subcutaneous or intravenous infusion. Can be administered as a separate infusion or by adding to opioid infusion/ PCA/NCA.
- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Injection (10mg/ml, 50mg/ml, 100mg/ml) and oral solution (50mg in 5ml) from a 'specials' manufacturer. Injection solution may be given orally. Mix with a flavoured soft drink to mask the bitter taste.

*CD*

- Schedule 2 CD.

## Ketorolac

### Use:

- Short-term management of moderate to severe acute postoperative pain
- Chronic pain: limited experience of extended use

### Doses and routes:

By intravenous or subcutaneous bolus

- **Child 1-15 years:** 500microgam/kg, maximum 15mg, repeated every 6 hours as required; maximum 60mg daily
- **16 years and over, body-weight over 50kg:** 10mg, every 4–6 hours as required: increased gradually to maximum of 90mg daily

By buccal route, using injection solution

- **Child 1 year and over:** 500micrograms/kg, maximum 15mg, up to 4 times daily

By continuous subcutaneous infusion

- **Child 1-15 years:** 2mg/kg/24hours, maximum 60mg daily
- **16 years and over, body-weight over 50kg:** 60mg/24hours, increased gradually to a maximum of 90mg daily

### Notes:

- Non-opioid, NSAID and preferential COX-1 inhibitor with potent analgesic effects, but only moderate anti-inflammatory action. Potency approximately twice that of naproxen.

### Licensing

- 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. Not licensed for subcutaneous or buccal administration

### Therapeutics

- Limited, poor quality data for indications other than post-operative pain. Anecdotal reports of effectiveness for patients with bone pain unresponsive to oral NSAIDs. Use the lowest possible dose for the shortest possible time
- High risk of gastrointestinal toxicity: co-prescription of a proton pump inhibitor strongly recommended.

### Contraindications, cautions

- Contraindicated in 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.
- May mask fever and other signs of inflammation

#### *Side effects*

- May be associated with increased risk of thrombotic events (e.g. myocardial infarction, thrombotic stroke) in children.
- All NSAIDs are associated with gastro-intestinal toxicity. Ketorolac is in the highest risk group. Co-prescription of a proton pump inhibitor is strongly recommended
- Other potential side 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.

#### *Interactions*

- Anticoagulants (contraindicated as the combination may cause an enhanced anticoagulant effect); corticosteroids (increased risk of GI ulceration or bleeding); diuretics (risk of reduced diuretic effect and increase the risk of nephrotoxicity of NSAIDs); other potential nephrotoxic drugs.

#### *Pharmacokinetics*

- Onset of action 10-30mins IV/IM; maximal analgesia achieved within 1-2 hours and median duration of effect 4-6 hours.

#### *Renal impairment*

- Reduce dose or avoid.

#### *Administration*

- For administration by intravenous bolus administer neat or diluted in a small volume of 0.9% sodium chloride or 5% dextrose and give over at least 15 seconds
- Subcutaneous injection can be irritant therefore dilute to the largest volume possible (0.9% sodium chloride suggested). Alkaline in solution so high risk of incompatibility if mixed with acidic drugs. Some data for compatibility in 0.9% sodium chloride with diamorphine or oxycodone. **Incompatibilities** include with cyclizine, glycopyrronium, haloperidol, levomepromazine, midazolam and morphine.

#### *Available as*

- Injection 30mg/ml (injection contains ethanol as an excipient) and injection 10mg/ml.

## Lactulose

### Use:

- Constipation, faecal incontinence related to constipation.
- Hepatic encephalopathy (portal systemic encephalopathy) and coma.

### Dose and route:

#### Constipation:

By mouth:

- **Neonate:** 2.5ml twice daily, adjusted according to response
- **Child 1 month-11 months:** 2.5ml twice daily, adjusted according to response
- **Child 1-4 years:** 2.5-10ml twice daily, adjusted according to response
- **Child 5 years and over:** 5-20ml twice daily, adjusted according to response

#### Hepatic encephalopathy:

By mouth

- **12 years and over:** 30-50ml three times daily, adjusted to produce 2-3 soft stools per day

### Notes:

- Osmotic laxative

#### *Licensing*

- Licensed for constipation in all age groups. Not licensed for hepatic encephalopathy in children.

#### *Therapeutics*

- Prebiotic: increases beneficial colonic bacteria (unlike macrogol). Macrogols are often preferable in palliative care but lactulose can be useful if large volumes are not tolerated. Generally unhelpful in opioid-induced constipation when a stimulant laxative is needed. Sickly taste. Unlikely to affect diabetic or ketogenic diets at conventional doses.

#### *Contraindications, cautions*

- Contraindicated in galactosaemia, intestinal obstruction.
- Caution in lactose intolerance.

#### *Side effects*

- Nausea, flatus, colic especially at high doses.

*Pharmacokinetics*

- Onset of action 36-48 hours.

*Administration*

- May be taken with water and other drinks. Dilute with 2-3 times the volume of water for administration via feeding tube. Therapeutic effect is unaffected by administration directly into the stomach or jejunum

*Patient information*

- See Medicines for Children leaflet: "Lactulose for constipation"  
<https://www.medicinesforchildren.org.uk/medicines/lactulose-for-constipation/>

*Available as*

- Oral solution

## Lansoprazole

### Use:

- Gastro-oesophageal reflux disease; erosive oesophagitis; prevention and treatment of NSAID induced gastric and oesophageal irritation; treatment of duodenal and gastric ulcer.
- Fat malabsorption despite pancreatic enzyme therapy in cystic fibrosis

### Dose and routes:

By mouth

- **Child body-weight less than 30 kg:** 500micrograms/kg-1mg/kg, maximum 15mg, once daily in the morning
- **Child body-weight more than 30 kg:** 15-30mg once daily in the morning

### Notes:

Gastric proton pump inhibitor

#### *Licensing*

- Not licensed in the UK for infants, children or adolescents. Licensed in the US from 1 year of age. Exact doses limited by available formulations.

#### *Therapeutics*

- Inhibition of gastric acid production is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Infants and children appear to need a higher mg/kg dose to achieve therapeutic acid suppression

#### *Cautions*

- FasTabs contain aspartame and should be used with caution in known PKU patients.

#### *Side effects*

- 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. Hypomagnesaemia may develop with prolonged use. PPIs are an independent 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.

#### *Pharmacokinetics*

- Oral bioavailability is good at 80-90% compared to 60% for omeprazole. Food slows down the absorption and decreases the bioavailability.



### *Hepatic impairment*

- Reduce by 50% in moderate to severe hepatic impairment

### *Interactions*

- Lansoprazole may interfere with absorption of drugs where bioavailability is significantly affected by gastric pH (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.

### *Administration*

- Anecdotal evidence for halving Lansoprazole FasTabs to give a 7.5mg dose. For optimal effect, the single daily dose is best taken in the morning. Lansoprazole should be taken at least 30 minutes before food.
- Capsules: Capsules should be swallowed whole with liquid. 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. FasTabs can be swallowed whole with water or mixed with a small amount of water if preferred.
- Lansoprazole FasTabs can be dispersed in 10 ml 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. Administration into the jejunum is unlikely to reduce bioavailability.

### *Patient information*

- See Medicines for Children leaflet: Lansoprazole for gastro-oesophageal reflux disease (GORD) and ulcers <https://www.medicinesforchildren.org.uk/medicines/lansoprazole-for-gastro-oesophageal-reflux-disease-gord-and-ulcers/>

### *Available as*

- Capsules 15mg and 30mg and orodispersible tablets 15mg and 30mg.

## Levetiracetam

### Use:

- Focal seizures with or without secondary generalisation
- Epilepsy; maintenance treatment
- Convulsive status epilepticus

### Dose and route:

#### Epilepsy: maintenance treatment

- Monotherapy of focal seizures with or without secondary generalisation
- Adjunctive therapy of focal seizures with or without secondary generalisation
- Adjunctive therapy of myoclonic seizures and tonic clonic seizures

By mouth or intermittent intravenous or subcutaneous infusion.

- **Child 1-5 months:** 7mg/kg once daily increased every 2 weeks in steps of up to 7mg/kg twice daily, maximum 21mg/kg per dose, twice daily
- **6 months-17 years (body-weight up to 50 kg):** Initially 10mg/kg once daily, then increase in steps of up to 10mg/kg twice daily (maximum per dose 30mg/kg twice daily). Dose to be increased every 2 weeks
- **18 years and over or body-weight 50 kg and above:** 250mg once daily increased every 2 weeks in steps of 250mg twice daily (maximum per dose 1.5 g twice daily).

By continuous subcutaneous or intravenous Infusion

- Administer total daily oral or intravenous dose of levetiracetam as a continuous infusion/24hours

#### Convulsive status epilepticus

- APLS resuscitation guideline (2021) first choice long-acting anticonvulsant after 2 doses of benzodiazepine
- Full loading dose to be given EVEN if the child is already receiving maintenance levetiracetam

By intravenous or interosseous injection over 5 minutes

- **Child 1 month and over:** 40mg/kg, maximum 3g  
Dilute 1:1 with 0.9% sodium chloride, minimum volume 10ml

## Notes:

### *Licensing*

- Not licensed for convulsive status epilepticus. Granules not licensed for use in children under 6 years, for initial treatment in children with body-weight less than 25kg, or for the administration of doses below 250mg.

### *Therapeutics*

- Phenobarbital, not levetiracetam, remains drug of first choice long acting anticonvulsant after 2 doses of benzodiazepine for neonatal seizures
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

### *Side effects*

- Movement disorders, sedation, confusion, exacerbation of seizures, neuroleptic malignant syndrome

### *Interactions*

- Caution when administering with other drugs with CNS depressant effects: decreases the clearance of Methotrexate

### *Administration*

- Intravenous administration over 15 minutes at a suggested concentration of 2.5-15mg/ml. May be administered at a concentration of 50mg/ml over 5-15 minutes in an acute situation.
- Administration of levetiracetam by subcutaneous bolus or intermittent (over 15-30 minutes) or continuous subcutaneous infusion is off-label but with increasing supporting (low-grade) evidence.
- Dose conversion for oral:intravenous:subcutaneous is 1:1:1
- Continuous subcutaneous infusion: Injection has a low pH and high osmolality which increases the potential for irritation around the injection site. Dilute in water for injections or 0.9% sodium chloride to the maximum volume compatible with the infusion device. May be administered neat i.e. at a concentration of 100mg/ml but increased risk of site reactions.
- Limited compatibility data. Administer via a separate syringe driver where possible. Reported to be visually compatible at usual concentrations with diamorphine, hyoscine butylbromide, levomepromazine, midazolam, morphine or oxycodone. Seek specialist advice.

### *Patient information*

- See Medicines for Children leaflet "Levetiracetam for preventing seizures"  
<https://www.medicinesforchildren.org.uk/medicines/levetiracetam-for-preventing-seizures/>

### *Available as*

- Tablets 250mg, 500mg, 750mg and 1g; oral solution 100mg/ml; solution for infusion 100mg/ml. Also available as granule sachets for oral administration 250mg, 500mg, 750mg, 1g, 1.5g

## Levomepromazine

### Use:

- Broad spectrum antiemetic where cause is unclear, or where probably multifactorial
- Second line if a specific antiemetic fails
- Antipsychotic and anxiolytic
- Sedation for terminal agitation
- Adjuvant for neuropathic pain

### Dose and routes

#### Nausea and vomiting

By mouth:

- **Child 1 month-11 years:** 50-100micrograms/kg once daily, usually at night, or in two divided doses.

Increase as required and tolerated in increments of 50–100micrograms/kg/24hours to a maximum of 400micrograms/kg/24hours.

- **12 years and over:** 2.5–5mg once daily, usually at night, or in two divided doses.

Increase as required and tolerated in increments of 2.5–5mg to maximum of 25mg/24hours

By continuous intravenous or subcutaneous infusion over 24hours:

- **Child 1 month-11 years:** 100micrograms/kg/24hours. Increase as necessary to a maximum of 400micrograms/kg/24hours. Maximum dose 25mg/24hours
- **12 years and over:** 5mg/24hours. Increase as necessary to a maximum of 25mg/24hours

Infusion doses can also be given as intermittent intravenous or subcutaneous boluses in one or two divided doses

#### Sedation and confusion, refractory pain

By continuous subcutaneous or intravenous infusion over 24hours:

- **Child 1 year-11 years:** 350micrograms/kg/24hours, maximum initial dose 12.5mg, increasing as necessary up to 3mg/kg/24hours
- **12 years and over:** 12.5mg/24hours increasing as necessary up to 200mg/24hours.

Infusion doses can also be given as intermittent intravenous or subcutaneous boluses in one or two divided doses

**Notes:**

- Phenothiazine antihistamine with powerful sedative and antiemetic properties

*Licensing*

- Licensed for use in children with terminal illness for the relief of pain and accompanying anxiety and distress

*Therapeutics*

- Injection solution has also been given sublingually in adults using the same doses as oral route
- A low dose is often effective as an antiemetic. Higher doses are very sedative and not necessarily more effective as an antiemetic. Consider adding an additional antiemetic with a different mode of action e.g. dexamethasone, ondansetron.

*Cautions*

- May lower seizure threshold. Caution in cardiac disease, liver and renal impairment.
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval

*Side effects*

- Hypotension, particularly with higher doses. Very sedating, especially at high doses.
- Paradoxical agitation, movement disorders including neuroleptic malignant syndrome.
- Constipation, vomiting

*Pharmacokinetics*

- Oral bioavailability 50%; consider halving dose if converting oral to subcutaneous or intravenous route in stable patient

*Renal impairment*

- Reduce dose and administer once daily in severe renal impairment, titrating according to response

*Interactions*

- Potent inhibitor of cytochrome P450 enzyme CYP2D6. May increase levels of drugs metabolised by this enzyme including amitriptyline.

*Administration*

- Tablets may be halved or quartered to obtain smaller doses. Tablets/segments may be dispersed in water for administration via a NG or gastrostomy tube. Flush tube well after administration. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Dilute in sodium chloride 0.9% or water for injection for subcutaneous infusion. Anecdotally associated with an increased risk of site reactions.

*Available as*

- Tablets (25mg) and injection (25mg/mL).

## Lidocaine (Lignocaine) plaster

### 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
- **Adult 18 years and over:** Apply up to 3 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period

### Notes:

#### *Licensing*

- Not licensed for use in children or adolescents under 18 years. Doses extrapolated from adult BNF

#### *Therapeutics*

- Lidocaine in the plaster diffuses continuously into the skin, providing a local analgesic effect. Putative mechanism of action: stabilisation of neuronal membranes by down-regulation of sodium channels
- Adult recommended maximum 3 plasters per application.
- 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 is similar for single and multiple administrations.
- An adequate treatment period is a minimum of 4 weeks in duration. Consider discontinuation if no response. For long-term use, treatment should be reviewed regularly to assess whether the number of plasters required can be reduced or the plaster-free period extended.
- Application to the head may be tolerated less well compared with the trunk and extremities.

#### *Cautions*

- Caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.

#### *Side effects*

- 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.

*Administration*

- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes. The plasters must be used within 14 days of opening the sachets.

*Available as*

- 700mg/medicated plaster (5% w/v lidocaine)

## Loperamide

### Use:

- Diarrhoea from non-infectious cause
- Faecal incontinence
- Management of high ileostomy output

### Dose and routes for management of chronic diarrhoea

By mouth:

- **Child 1-11 months:** 100micrograms/kg twice daily given 30 minutes before feeds. Increase as necessary up to a maximum of 1.25mg/kg/day given in divided doses
- **Child 1-11years:** Initial dose of 100micrograms/kg, maximum single dose 2mg, 3-4 times daily. Increase as necessary up to a maximum of 1.25mg/kg/day in divided doses, maximum 16mg total daily dose
- **12 years and over:** Initial dose of 2mg 2-4 times daily. Increase as necessary up to a maximum of 16mg/day in divided doses.

### Notes

#### *Licensing*

- Not licensed for use in children with chronic diarrhoea. Capsules not licensed for use in children under 8 years. Syrup not licensed for use in children under 4 years.

#### *Therapeutics*

- Maximum therapeutic impact may not be seen for 16-24 hours.
- BNFC quotes a maximum of 2mg/kg/day in divided doses for children aged 1-11 months. However APPM has been unable to identify evidence of sufficient quality to justify this recommendation.
- Despite low bioavailability (due to almost complete first pass metabolism primarily by CYP3A4), some loperamide may be absorbed leading to life threatening toxicity in patients treated with very high doses, above the recommended maximum, for high output diarrhoeal or stoma losses

#### *Side effects*

- Constipation, nausea, flatulence.

#### *Administration*

- Orodispersible tablets can be dissolved in water. Disperse one orodispersible tablet in 4mL of water for a 0.5mg/mL suspension. For proportional doses, draw up the required dose and administer immediately. Resulting suspension can be administered without risk of blocking feeding tubes. Flush well after administration.
- Jejunal administration will not affect the therapeutic response to loperamide.



*Patient information*

- See Medicines for Children leaflet “Loperamide for diarrhoea”  
<https://www.medicinesforchildren.org.uk/medicines/loperamide-for-diarrhoea/>

*Available as*

- Tablets (2mg), capsules (2mg), orodispersible tablets (2mg).

## Lorazepam

### Use

- Anxiety, including anxiety associated with dyspnoea
- Agitation and distress
- Adjuvant in cerebral irritation
- Muscle spasm
- Anticipatory nausea and vomiting in chemotherapy
- Status epilepticus

#### Important safety information

#### **For all benzodiazepines**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### **Anxiety, agitation, cerebral irritability, muscle spasm, anticipatory nausea and vomiting**

By mouth:

- **Child 1-11 months:** 25micrograms/kg 2–3 times daily
- **2-5 years:** 500micrograms 2–3 times daily
- **6-10 years:** 750micrograms 3 times daily
- **11-14 years:** 1mg 3 times daily
- **15 years and over:** 1–2mg 3 times daily.

By buccal route:

- **Child 1 month and over:** 25micrograms/kg as a single dose, as required 2-3 times daily. Increase to 50micrograms/kg, maximum 1mg/dose, if necessary

- **Adult:** 500micrograms–1mg as a single dose, repeat as required.

### Status epilepticus

By slow intravenous injection:

- **Neonate:** 100micrograms/kg/dose repeated after 10 minutes if required
- **Child 1 month-11 years:** 100micrograms/kg/dose, maximum 4mg, repeated after 10 minutes if required
- **12 years and over:** 4mg repeated after 10 minutes if required.

### Notes

#### *Licensing*

- Licensed in children for 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.

#### *Therapeutics*

- Potency in the order of 10 times that of diazepam per mg as anxiolytic/sedative.

#### *Cautions*

- May cause drowsiness and respiratory depression if given in large dose. Half-life 10–20 hours therefore risk of accumulation with frequent PRN doses. Caution in renal and hepatic failure.

#### *Pharmacokinetics*

- Well absorbed buccally with rapid onset of effect. There may however be variable absorption by this route with further variation possible depending on the formulation used.

#### *Administration*

- Specific buccal tablets are not available in the UK but generic lorazepam tablets (specifically Genus, PVL or TEVA brands) do dissolve in the mouth so can be given buccally. Tablets may be dispersed in water for administration via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

#### *Available as*

- Tablets (250micrograms 500micrograms, 1mg, 2.5mg) and injection (4mg/ml), oral solution (1mg/ml: Licensed in UK but not licensed for use in children, expensive and contains significant quantity of ethanol as an excipient)

#### *CD*

- CD Schedule 4

## Macrogols

### Use

- Constipation.
- Faecal impaction.
- Suitable for opioid-induced constipation.

### Dose and route:

#### Constipation, prevention of opioid-induced constipation

By mouth

Using paediatric (or half adult-size) sachets for those less than 12 years of age

- **Child under 1 year:** ½-1 paediatric sachet daily
- **Child 1-5 years:** 1 paediatric sachet daily (adjust dose according to response; maximum 4 paediatric sachets daily)
- **Child 6-11 years:** 2 paediatric sachets daily (adjust dose according to response; maximum 4 paediatric sachets daily)
- **12 years and over:** 1–3 adult sachets daily.

Using Movicol® liquid:

- **12 years and over:** 25 mL 1–3 times daily usually for up to 2 weeks; maintenance 25 mL 1–2 times daily.

Using Movicol® ready to take sachets:

- **12 years and over:** 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily.

### Faecal impaction

By mouth:

Using paediatric (or half adult-size) sachets for those less than 12 years of age

- **Child under 1 year:** ½-1 paediatric sachet daily

- **Child 1-4 years:** 2 paediatric 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 paediatric 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
- **12 years and over:** 4 adult sachets on first day, 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

Osmotic laxative

### *Licensing*

- Not licensed for use in children under 5 years with faecal impaction and under 2 years with chronic constipation.

### *Therapeutics*

- Increased stool volume stimulates peristalsis, however no inherent stimulant action. Ensure adequate hydration.

### *Cautions*

- Ready to take sachets have higher concentrations of electrolytes including sodium and potassium. Caution if fluid or electrolyte disturbance. Caution with high doses (volumes) in those with impaired gag reflex, reflux oesophagitis or impaired consciousness.

### *Administration*

- Manufacturer advises dilute 25 ml of oral concentrate with 100 ml of water; after dilution the solution should be discarded if unused after 24 hours. 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 administration. Efficacy unlikely to be affected by jejunal administration

### *Patient information*

- See Medicines for Children leaflet "Movicol for constipation" "<https://www.medicinesforchildren.org.uk/medicines/movicol-for-constipation/>

### *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 an oral liquid concentrate (dilute with water before administration) and 25ml oral solution sachets.

## Melatonin

### Use:

- Sleep disturbance due to disruption of circadian rhythm (not anxiolytic).

### Dose and route:

By mouth:

- **Child 1 month and over:** 2–3mg at night, increasing every 1–2 weeks dependent on effectiveness up to maximum 10mg.

### Notes:

#### *Licensing*

- Adaflex® immediate release tablets, Ceyesto® 3mg prolonged release tablets and Colonis® melatonin liquid 1mg/ml are licensed for treatment of insomnia in children with ADHD from 6 years of age. Slenyto® is licensed in children and adolescents aged 2-18 years with Autism Spectrum Disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. All other melatonin formulations are not licensed for use in children.

#### *Therapeutics*

- Treatment should be initiated by a specialist. Ensure appropriate attention to sleep hygiene. Some prescribers use a combination of immediate-release and modified release tablets to optimise sleep patterns.
- Maximum doses are frequently outside the individual product licences

#### *Cautions*

- Caution when switching between immediate-release formulations as the peak plasma melatonin concentration may be higher with the oral solution than with tablets. Intake with carbohydrate-rich meals may impair blood glucose control.
- Reduced clearance in hepatic impairment.

#### *Interactions*

- Metabolised by cytochrome P450 enzyme CYP1A2. Levels may be increased by drugs that inhibit this enzyme including ciprofloxacin. Levels may be reduced by drugs that induce this enzyme including phenytoin.

#### *Administration*

- Modified-release tablets should be taken with or after food. The modified-release tablet Slenyto® may be mixed whole into food or drink (e.g. yoghurt, orange juice, or ice-cream) immediately before administration. Licensed immediate-release formulations should be taken on an empty stomach, 2 hours before or 2 hours after food. The immediate-release tablet Adaflex® may be crushed and mixed with water immediately before administration. Use oral liquid for administration via an enteral feeding tube No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children leaflet: Melatonin for sleep disorders  
<https://www.medicinesforchildren.org.uk/medicines/melatonin-for-sleep-disorders/>

*Available as*

- Prolonged release mini-tablets 1mg, 5mg (Slenyto®), prolonged release tablets 2mg, 3mg (various), immediate release tablets 1mg, 2mg, 3mg, 4mg, 5mg (Adaflex®), oral solution 1mg/1ml (Colonis®)

## Methadone

### Use:

- Moderate to severe pain, particularly neuropathic pain and pain poorly responsive to other opioids.
- Not normally used as first line analgesia in the UK

Extremely important safety information

Methadone should only be commenced by practitioners experienced in its use.

This is due to wide inter-individual variation in response, very variable conversion ratios with other opioids, complex pharmacokinetics and a long half-life.

Initial close monitoring is particularly important.

Important safety information

### For all opioids

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### **Pain in patients already receiving regular strong opioids**

By mouth:

Convert using *specific protocols* from previous opioid analgesia

**Caution:** Converting a patient to methadone from another opioid analgesic 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.



Consider other opioids first before rotating from morphine to methadone due to unacceptable side effects or inadequate analgesia. Consultation with a pain clinic or specialist palliative care service is advised

It can be difficult to convert a short or long-acting opioid to an equivalent dose of methadone. Current practice is usually to admit to a specialist inpatient unit or titrate orally at home with very close supervision. Close monitoring should be continued for a period of two weeks.

### ***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 equianalgesic ratio increases as the dose of morphine increases.

### ***Protocols for converting patients to methadone***

In adults there are several protocols for converting patients to methadone. These are not evidence based in paediatrics.

- *The reduce-and-replace* (also known as 3-day switch) protocol incorporates a transition period where the dose of the former opioid is reduced and partially replaced by methadone. The methadone dose is then titrated upwards. This approach is considered safer and may be more effective.
- *The rapid-conversion* (also known as regular-dose or stop-and-go), protocol advocates stopping previous opioid therapy completely and then starting a fixed dose of methadone at regular intervals.

**Reduce-and-replace protocol**

1. Calculate the average total daily oral morphine equivalent (OME)

Add up the patient's total oral opiate requirement over the previous 48 hours. Use the equianalgesic table (Appendix 1) to calculate the oral morphine equivalent (OME). Do not include breakthrough doses for incident pain. Divide by two to give the average total daily OME

2. Convert the average total daily OME to the approximate equianalgesic dose of methadone using the table below

Total daily OME	Equianalgesic ratio morphine(mg):methadone(mg) Divide by this ratio
Less than 90mg/day	4:1
90-299mg/day	6:1
300-599mg/day	8:1
600-799mg/day	12:1
800mg/day or more	15:1

3. Replace original opioid with methadone, stepwise over 3 days
  - *Day 1* replace 1/3 of original opioid with equianalgesic dose of methadone in 3 divided doses
  - *Day 2* replace 2/3 of original opioid with equianalgesic dose of methadone in 3 divided doses
  - *Day 3* onwards replace all of original opioid with equianalgesic dose of methadone in 3 divided doses
4. Consider reducing the dose of methadone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

**Example:**

Total daily OME = 900mg/day

Equianalgesic ratio for total daily OME of 900mg/day = 15:1 (from the table above)

Divide OME by equianalgesic ratio to obtain equianalgesic dose of methadone

900mg/day OME ÷ 15/1 = 60mg methadone

Reduce the dose of methadone by 50% as the patient is already on a high dose of the previous opioid

60mg methadone x 50% = 30mg methadone

Day 1: Give 2/3 original opioid (OME 600mg) and 1/3 equianalgesic dose of methadone in 3 divided doses

=  $30\text{mg} \div 3 = 10\text{mg}$  methadone in 3 divided doses

=  $10\text{mg}$  methadone  $\div 3 = 3.3\text{mg}$  methadone three times daily

Day 2: Give 1/3 original opioid (OME 300mg) and 2/3 equianalgesic dose of methadone in 3 divided doses

=  $30\text{mg} \div 3 = 10\text{mg}$  methadone in 3 divided doses

=  $10\text{mg}$  methadone  $\div 3 \times 2 = 6.6\text{mg}$  methadone three times daily

Day 3: Stop original opioid and give full equianalgesic dose of methadone in 3 divided doses

=  $30\text{mg} \div 3 = 10\text{mg}$  methadone three times daily

5. Use an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain. It may also be necessary to reduce the breakthrough dose by 25-50%
6. 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.
7. To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 20% 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.
8. If excess sedation occurs reduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission

### ***Rapid-conversion-protocol***

1. Calculate the average total daily oral morphine equivalent (OME)

Add up the patient's total oral opiate requirement over the previous 48 hours. Use the equianalgesic table (Appendix 1) to calculate the oral morphine equivalent (OME). Do not include breakthrough doses for incident pain. Divide by two to give the average total daily OME

2. Convert the adjusted total daily OME (from step 1 above) to the equianalgesic dose of oral methadone by dividing by 15 (most guides say 10 so this is a cautious approach).
3. Consider reducing the dose of methadone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation
4. Calculate the initial methadone dose by dividing the equianalgesic dose of methadone (from step 3 above) by 3.

The initial dose would not normally exceed

- **Child body-weight less than 50kg:** 5mg three times daily
- **Body-weight 50kg and over:** 10mg three times daily

If converting from a long-acting opioid, give the first methadone dose 6 hours after the last long-acting opioid dose or 10-12 hours after opioid patch removal.

*Example:*

Total daily OME = 900mg/day

900mg/day OME ÷ 15 = 60mg methadone

Reduce the dose of methadone by 50% as the patient is already on a high dose of the previous opioid

60mg methadone x 50% = 30mg methadone

Calculate the initial methadone dose by dividing the equianalgesic dose of methadone by 3

= 30mg ÷ 3 = 10mg three times daily

5. Use an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain. It may also be necessary to reduce the breakthrough dose by 25-50%
6. 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.
7. To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 20% 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.

8. If excess sedation occurs reduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission.

By intermittent intravenous injection, continuous subcutaneous infusion, or continuous intravenous infusion:

Convert from previous opioid analgesia using appropriate methadone conversion protocol if applicable

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose of oral methadone administered over the previous 24 hours

Divide the total daily dose of oral methadone by two and administer by continuous infusion

Ensure continued access to immediate release morphine as required for breakthrough pain

Alternatively, the total daily dose of intravenous or subcutaneous methadone can be given as a single intravenous bolus injection over 3-5minutes or 2-3 divided doses

Seek specialist guidance if mixing with any other drug.

### **Pain in opioid naïve patients**

By mouth:

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child 1-12 years:** 50-100micrograms/kg/dose, maximum 2.5mg, 2-3 times daily
- **12 years and over:** 2.5mg/dose, 2–3 times daily

Methadone has a long and variable half-life with potential to cause sedation, respiratory depression and even death from secondary peak phenomenon.

Consider using an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain.

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 very cautious and usually by no more than 20% 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.

If excess sedation occurs reduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission.

### **Notes:**

- Strong opioid with  $\mu$ -opioid receptor agonist, and NMDA-receptor-channel blocker properties

### *Licensing*

- Not licensed for use in children.

### *Therapeutics*

- Methadone is a racemic mixture: L-isomer, analgesic active (levomethadone; L-polamidon®); R-isomer unknown action.
- In some countries levomethadone is available. It has a different strength to methadone.
- Partial replacement of former opioid is sometimes used if completing the full switch produces intolerable adverse effects: however completing the switch rather than using a combination of opioids is recommended in the first instance
- A naloxone infusion should be used to treat methadone overdose in view of the long and variable half-life
- Respiratory depressant effects may last longer than analgesic effects.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

### *Cautions*

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval

### *Monitoring*

- Following concerns regarding methadone and sudden death from prolongation of QT-interval or Torsades 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 with methadone.

### *Side effects*

- Usual strong opioid side effects.
- Also associated with prolonged QT-interval and ventricular arrhythmia (torsade de pointes)

### *Pharmacokinetics*

- Limited data in paediatric patients; known to have wide inter-individual variation.
- Newer evidence suggests oral bioavailability may be as much as 80%

*Hepatic impairment, renal impairment*

- Reduce methadone dose by 50% in severe renal impairment and titrate according to response.
- Significant accumulation is unlikely in renal failure, as elimination is primarily via the liver.
- Avoid in severe hepatic impairment

*Interactions*

- Opioid antagonists naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent patients. Naloxone will antagonise the analgesic, CNS and respiratory depressant effects of methadone.
- Metabolised by cytochrome P450 enzymes CYP2B6 and CYP3A4. Levels increased by drugs that inhibit these enzymes including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels may be reduced by drugs that induce these enzymes including carbamazepine, phenobarbital and phenytoin.

*Administration*

- If CSCI methadone causes a skin reaction, consider doubling the dilution and changing the syringe every 12 hours
- Use liquid preparations for administration via feeding tube. Absorption of methadone is unlikely to be affected by jejunal administration.

*Available as*

- Linctus (2mg/5ml), mixture (1mg/ml), oral solution (1mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml), tablets (5mg), and injection (10mg/ml, 50mg/ml, 50mg/2 ml).

*CD*

- CD schedule 2.

## Methylnaltrexone

### Use:

- Opioid-induced constipation when the response to other laxatives alone is inadequate and other relevant factors have been or are being addressed.

### Dose and routes

By intermittent subcutaneous (or intravenous) bolus:

- **Child 1 month- 12 years or body weight less than 38kg:** 150micrograms/kg, maximum 8mg, as a single dose
- **Over 12 years, body-weight 38-61kg:** 8mg as a single dose
- **Over 12 years and body-weight over 61kg:** 12mg as a single dose

A single dose may be sufficient: repeat doses may be given with a usual administration schedule of a single dose every other day.

Doses may be given at 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.

### Notes:

- $\mu$ -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.

#### *Licensing*

- Not licensed for use in children or adolescents less than 18 years. Licensed for subcutaneous but not intravenous administration in adults.

#### *Therapeutics*

- Constipation in palliative care is usually multifactorial and other laxatives are often required in addition: continue all other laxative treatment.
- May also improve other peripheral effects of opioids, e.g. delayed gastric emptying, urinary retention. Case reports also suggest benefit in cholestatic pruritus.
- Does not cross blood brain barrier.
- Onset of action may be within 15-60 minutes: 30-50% patients have a bowel movement within 4 hours, without loss of analgesia.
- Has been used orally in adults, using a specially formulated tablet preparation, at doses of up to 450mg daily

#### *Contraindications, cautions*

- Contraindicated in known or suspected bowel obstruction other than that caused by opiate-induced constipation.



*Side effects*

- Common: abdominal pain/colic, diarrhoea, flatulence and nausea.

*Renal impairment*

- Reduce dose by 50% in severe renal impairment.

*Administration*

- Rotate the site of subcutaneous injection. Do not inject into areas where the skin is tender, bruised, red or hard.

*Available as*

- Single use vial 12mg/0.6ml solution for SC injection (Relistor®)

## Metoclopramide

### Use

- Prokinetic anti-emetic, in gastric compression or gastroparesis
- Hiccups

### Dose and route:

By mouth, intramuscular, subcutaneous or slow intravenous injection

- **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 daily).

Total daily dose may be administered as a continuous subcutaneous or intravenous infusion/24hours

### Notes:

#### *Licensing*

- Not licensed for use in infants less than 1 year of age. Tablets not licensed for use in under 15 years (body-weight less than 61 kg). Not licensed for continuous infusion.

#### *Therapeutics*

- Efficacy comparable to domperidone in gastroparesis but higher incidence of adverse effects
- Use in palliative care only when alternative treatments do not work or cannot be used.
- Treatment should be limited to short term use (up to 5 days) if at all possible
- Has also been used in refractory hiccup not responsive to physical measures, or first line medication

#### *Contraindications, cautions*

- Contraindicated in children younger than 1 year, except in palliative care where no other alternative is available.
- Epilepsy: increased frequency and severity of epileptic seizures
- The EMA (2013) recommends that, due to the risk of neurological side effects, metoclopramide should only be used in children aged 1-18 as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established postoperative nausea and vomiting, and only when other treatments do not work or cannot be used.

#### *Side effects*

- Acute dystonic reactions including muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. Dystonic effects usually occur shortly after starting treatment and subside within 24 hours of discontinuation. Acute dystonic reactions can be effectively reversed using anticholinergics e.g. procyclidine and/or benzodiazepines e.g. diazepam.
- Neuroleptic malignant syndrome

- Risk of extrapyramidal effects is dose related and increased with co-administration of other drugs known to cause extrapyramidal effects

*Administration*

- 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. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

*Available as*

- Tablets (10mg), oral solution (5mg/5ml) and injection (5mg/ml).

## Metronidazole topically

### Use:

- Reduction of odour caused by anaerobic bacteria associated with wounds or fungating tumours

### Dose and route:

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:

#### *Licensing*

- Off label use. Anabact® not licensed for use in children under 12 years.
- Metrogel® not licensed for use with children.

#### *Administration*

- Avoid eye area due to stinging.

#### *Available as*

- Cream and gel (Anabact® 0.75%, Metrogel® 0.75%).

## Miconazole oral gel

### Use:

- Oral and intestinal fungal infection.

### Dose and route:

#### Prevention and treatment of oral candidiasis

By mouth:

- **Neonate:** 1ml 2-4 times daily smeared around inside of mouth after feeds.
- **Child 1- 23 months:** 1.25 ml 4 times daily smeared around inside of mouth after food
- **Child 2 years and over:** 2.5 ml 4 times daily after meals

Continue treatment for at least 7 days after lesions have healed or symptoms have disappeared.

#### Prevention and treatment of intestinal candidiasis

By mouth:

- **Child 4 months and over:** 5mg/kg 4 times daily; max. 250mg (approximately 10 ml) 4 times daily.

### Notes:

#### *Licensing*

- Not licensed for use in children under 4 months or during the first 5-6 months of life of an infant born preterm.
- Muco-adhesive tablet licensed in USA for child over 16 years.

#### *Contraindications, cautions*

- Contraindicated in infants with impaired swallow.

#### *Interactions*

- Increased INR/ bleeding has been reported with concomitant use of buccal miconazole and oral anticoagulants.

#### *Administration*

- Avoid applying near the back of the throat in infants and babies due to choking risk
- Retain in the mouth near lesions for as long as possible before swallowing.
- 50mg muco-adhesive buccal tablets should be applied to the upper gum just above the incisor tooth once daily for 7-14 days.
- Orthodontic appliances should be removed at night and brushed with gel.

#### *Available as*

- Oral gel (20mg per gram or 124mg per 5ml approximately 24mg/ml) in 15g and 80g tube, orange flavour. 15g oral gel can be brought over the counter
- A muco-adhesive buccal tablet of miconazole is now available. Indicated for the treatment of oropharyngeal candidiasis in immunocompromised adults, Loramyc®

## Midazolam

### Use:

- Status epilepticus and terminal seizure control.
- Conscious sedation for procedures, to minimise awareness in terminal haemorrhage
- Management of anxiety/agitation associated with symptoms at the end of life.
- Anxiety associated with dyspnoea.
- Adjuvant for pain of cerebral irritation.
- Dystonia rescue

Important safety information

#### **For all benzodiazepines**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

**Dose and route:****Status epilepticus**

	<b>By buccal or intranasal route:</b>	<b>By subcutaneous or slow intravenous bolus injection</b>	<b>By continuous intravenous or subcutaneous infusion for seizure control at end of life</b>
	Doses can be repeated once after an interval of at least 10 minutes		
<b>Neonate</b>	300microgram/kg, maximum 1.25mg/dose	200micrograms/kg/dose maximum 10mg/dose	1mg/kg/24hours increasing gradually to a maximum of 7mg/kg/24hours
<b>Child 1-2 months</b>	300microgram/kg, maximum 2.5mg/dose		1mg/kg/24hours Increasing gradually to a maximum of 7mg/kg/24hours, maximum 60mg/24hours
<b>3-11 months</b>	2.5mg/dose		Higher doses up to 150mg/24hours have been used. Seek specialist advice, and consider addition of other agents such as phenobarbital before increasing above 60mg/24hours.
<b>1-4 years:</b>	5mg/dose		
<b>5-9 years:</b>	7.5mg/dose		
<b>10 years and over</b>	10mg/dose		

**Conscious sedation e.g. for procedures, or to minimise awareness in terminal haemorrhage**

Doses can be repeated once after an interval of at least 10 minutes

	<b>By buccal or intranasal route:</b>	<b>By subcutaneous or slow intravenous bolus injection</b>	<b>By mouth</b>
<b>Neonate</b>	300microgram/kg, maximum 1.25mg/dose	200micrograms/kg/dose maximum 10mg/dose	500micrograms/kg/dose maximum 20mg
<b>Child 1-2 months</b>	300microgram/kg, maximum 2.5mg/dose		
<b>3-11 months</b>	2.5mg/dose		



<b>1-4 years</b>	5mg/dose		
<b>5-9 years</b>	7.5mg/dose		
<b>10 years and over</b>	10mg/dose		

### Anxiety, agitation at end of life, cerebral irritation, dystonia rescue

Doses refer to **starting** doses only

Age range <sup>22</sup>	Buccal <sup>23</sup>	Oral <sup>24</sup>	Intravenous or subcutaneous bolus <sup>25</sup>	Continuous intravenous or subcutaneous infusion <sup>26</sup>
<b>Neonate</b>	75microgram/kg Initial maximum 300micrograms/dose As required 6 -8 hourly, maximum 2 hourly	150micrograms/kg Initial maximum 600micrograms/dose As required 6 -8 hourly, maximum 2 hourly	50micrograms/kg Initial maximum 200micrograms/dose As required 6 -8 hourly, maximum 2 hourly	200micrograms/kg /24hours Initial maximum 800micrograms/24hours
<b>1-2 months (less than 5.5kg)</b>	75microgram/kg Initial maximum 500micrograms/dose As required 4-6 hourly, maximum hourly	150micrograms/kg Initial maximum 1mg/dose As required 4-6 hourly, maximum hourly	50micrograms/kg Initial maximum 300micrograms/dose As required 4-6 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 1.2mg/24hours
<b>3-11 months (5.6-9.9kg)</b>	500micrograms-1mg As required 4 hourly, maximum hourly	1.5mg As required 4 hourly, maximum hourly	50micrograms/kg Initial maximum 500micrograms/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 2mg/24hours
<b>1-4 years (10-17kg)</b>	1.5mg	2.5mg	50micrograms/kg Initial maximum 1mg/dose	200micrograms/kg over 24hours Initial maximum 4mg/24hours

<sup>22</sup> Aged based doses rounded to nearest 500micrograms for convenience of administration

<sup>23</sup> Based on 25% buccal seizure rescue dose

<sup>24</sup> Based on buccal bioavailability of 75% and oral bioavailability of 40%

<sup>25</sup> Based on 25% intravenous / subcutaneous seizure rescue dose

<sup>26</sup> Based on 4 x intravenous/subcutaneous dose for anxiety, agitation, breathlessness

Age range <sup>22</sup>	Buccal <sup>23</sup>	Oral <sup>24</sup>	Intravenous or subcutaneous bolus <sup>25</sup>	Continuous intravenous or subcutaneous infusion <sup>26</sup>
	As required 4 hourly, maximum hourly	As required 4 hourly, maximum hourly	As required 4 hourly, maximum hourly	
<b>5-9 years</b> (18kg-32kg)	2mg  As required 4 hourly, maximum hourly	3.5mg  As required 4 hourly, maximum hourly	50micrograms/kg  Initial maximum 1.5mg/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours  Initial maximum 6mg/24hours
<b>10 years and over</b> (over 32kg)	2.5mg  As required 4 hourly, maximum hourly	5mg  As required 4 hourly, maximum hourly	50microgram/kg  Initial maximum 2.5mg/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours  Initial maximum 10mg/24hours

## Notes

### Licensing

- The range of potential indications for midazolam in paediatric palliative care is very wide, but most are not licensed in infants or in children. See product literature.
- Oromucosal solution licensed only for seizure control in children 3 months of age and over. Midazolam injection is not licensed for oral or buccal administration. Midazolam injection licensed only for procedural sedation, anaesthesia and sedation in intensive care.

### Therapeutics

- Doses above derived from standard doses for epilepsy via buccal and intravenous routes, taking into account recommendations in adult palliative care, and available information on bioavailability and pharmacokinetics in neonates, children and adults
- Dose recommendations in adult palliative care have been reduced over time due to recognition that lower doses were as effective and resulted in fewer adverse effects. Dose recommendations take this into account however it is important to recognise that the population of patients receiving palliative care in the adult sector is not typical of the paediatric palliative care population
- Pharmacology in children is complex and not well understood. Clearance is increased in sick patients particularly those ventilated on PICU. Tolerance/clearance may be higher in young adult males and in those already receiving other benzodiazepines and other drugs that may increase metabolism. If in doubt, start at the lowest recommended dose and titrate rapidly.
- In single dose for seizures, buccal 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
- Patients receiving midazolam by continuous infusion should continue to have buccal and/or bolus midazolam available as required for breakthrough symptoms. The

background infusion can then be increased, no more often than every 12 hours, taking into account the requirement for breakthrough doses.

- Alternatively midazolam can be administered as a continuous patient controlled, patient-proxy controlled or nurse controlled infusion starting with a bolus dose equivalent to the hourly background rate and a lockout of between 5 and 15 minutes.
- Consider adding in an antipsychotic e.g. levomepromazine, before increasing midazolam above 600micrograms/kg/24hours or 30mg/24hours in agitation at end of life.

#### *Cautions*

- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency.

#### *Side effects*

- Both high and low doses can lead to paradoxical agitation.

#### *Pharmacokinetics*

- Buccal bioavailability will be lower if some of the dose is swallowed: this is more likely when used for indications other than status epilepticus, or larger volumes
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 minutes. Half-life 2-5 hours.
- 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.
- Half-life may be shorter in patients on enzyme inducing drugs or those already receiving benzodiazepines
- Repeated dosing within an hour leads to increased peak and AUC (area under the plasma drug concentration-time curve)
- Half-life in neonates may be longer due to hepatic immaturity
- Half-life may be much longer in sick patients especially those with multi-organ system failure or critically ill on intensive care, and obese patients

#### *Interactions*

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by inhibitors of this enzyme including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels reduced by inducers of this enzyme including carbamazepine, phenobarbital and phenytoin
- Fatalities have occurred after concurrent administration with higher than approved doses of olanzapine
- The addition of a CYP3A4 inducer may reduce midazolam levels by  $\leq 90\%$ . Use of a different benzodiazepine is recommended if a moderate or potent inducer is essential
- Plasma concentrations of midazolam can be eight times higher after the addition of a CYP3A4 inhibitor. Midazolam doses may need to be reduced by  $\geq 50\%$ .

#### *Administration*

- For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Anecdotal reports of oral solution or injection administered via buccal route
- If enteral tube administration is indicated, the oral liquid or injection can be used.

#### *Patient information*

- See Medicines for Children leaflet "Midazolam for stopping seizures"  
<https://www.medicinesforchildren.org.uk/medicines/midazolam-for-stopping-seizures/>

*Available as*

- *Injection* (1mg/ml, 2mg/ml and 5mg/ml). *Oral solution* (5mg/ml Miprosed® and Thame generic and 2mg/ml Ozalin®). *Buccal liquid* Pre-filled oral syringes (strength 5mg/ml) available as 10mg in 2ml, 7.5mg in 1.5ml, 5mg in 1ml and 2.5mg in 0.5ml (e.g. Buccolam®, generics). Pre-filled oral syringes (strength 10mg/ml) available as 10mg in 1ml, 7.5mg in 0.75ml, 5mg in 0.5ml and 2.5mg in 0.25ml (e.g. Epistatus)
- Epistatus is also available as an unlicensed special in a 5ml multidose bottle (strength 10mg/ml) which is very useful when small doses are required
- Other oral and buccal liquids may also be available from 'specials' manufacturers or specialist importing companies (unlicensed)
- The buccal and oral formulations available differ in strengths-take care with prescribing and administration

*CD*

- CD Schedule 3 (CD No Register). Local protocols may require safe storage..

## Morphine

### Use:

- Moderate to severe pain.
- Dyspnoea.

Important safety information

#### **For all opioids**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

**Dose and route:****Pain in opioid naïve patients**Doses refer to **starting** doses only<sup>27</sup>

Age range	By mouth or per rectum	Intravenous or subcutaneous bolus	Intravenous or subcutaneous infusion/24hours
<b>Neonate</b>	80micrograms/kg/dose 6 hourly	40micrograms/kg/dose 6 hourly	160micrograms/kg/24hours
<b>Child 1-2 months</b>	120micrograms/kg/dose 6 hourly	60micrograms/kg/dose 6 hourly	240micrograms/kg/24hours
<b>3-5 months</b>	120micrograms/kg/dose 4 hourly	60micrograms/kg/dose 4 hourly	360micrograms/kg/24hours
<b>6-23 months</b>	200micrograms/kg/dose 4 hourly	80micrograms/kg/dose 4 hourly	480micrograms/kg/24hours
<b>2-11 years</b>	200- 300micrograms/kg/dose maximum 10mg/dose 4 hourly	80- 100micrograms/kg/dose maximum 5mg/dose 4 hourly	480- 600micrograms/kg/24hours maximum 20mg/24hours
<b>12 years and over</b>	200micrograms/kg/dose maximum 10mg/dose 4 hourly  <i>Alternatively</i> 5-10mg/dose, 4 hourly	80- 100micrograms/kg/dose maximum 5mg/dose 4 hourly  <i>Alternatively</i> 2.5-5mg/dose, 4 hourly	480- 600micrograms/kg/24hours maximum 30mg/24hours  <i>Alternatively</i> 20-30mg/24hours

**Pain in patients already receiving regular strong opioids**

Convert using oral morphine equivalent (OME) from previous opioid analgesia, if applicable, see Appendix 1

By mouth using modified release preparations

- Calculate the total daily dose (regular + PRN) of oral morphine administered over the previous 24 hours once the patient is established on regular morphine for 2-3 days

*12 hourly preparations:* Divide the total daily dose of oral morphine by two and administer every 12 hours

*24 hourly preparations:* Administer the total daily dose of oral morphine every 24 hours

<sup>27</sup> Doses derived from primary research and cross referenced to BNFC ensuring age bands and dosing intervals are consistent, taking into account longer half-life in neonates and infants, equianalgesia, bio-availability via different routes, and ensuring consistent total daily dose across each age band

Ensure continued access to immediate release morphine as required for breakthrough pain see below

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of oral morphine administered over the previous 24 hours

Divide the total daily dose of oral morphine by **three** and administer by continuous infusion

Ensure continued access to immediate release morphine as required for breakthrough pain see below

### **Breakthrough Pain in patients already receiving regular strong opioids**

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10 to 1/6 of total daily morphine dose every 1-4 hours as required.
- Remember to convert dose if a different route is used for breakthrough and background e.g. CSCI with oral for breakthrough

Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

### **Dyspnoea, cough suppressant**

By mouth, subcutaneous or intravenous routes

- **Child 1 month and over:** 25-50% of pain doses

### **Notes:**

- Strong opiate of first choice by mouth and for intravenous or continuous subcutaneous infusion

### *Licensing*

- Oramorph® solution and MXL® capsules not licensed for use in children aged under 1 year. Sevredol® tablets not licensed for use in children under 3 years. MST Continus® preparations licensed to treat children with cancer pain (age-range not specified by manufacturer). Actimorph® orodispersible tablets not licensed for use in children under 6 months.

### *Therapeutics*

- Systematic review evidence suggests an equianalgesic oral to intravenous ratio of to 3:1 may be more appropriate than previously recommended ratio of 2:1.
- Some adult centres advocate giving patients on regular immediate release morphine a double dose of morphine immediate release at bed-time. This appears to be safe and reduces the likelihood of the patient waking overnight in pain.
- Can be used as a cough suppressant when treating the underlying cause is either not helpful or not possible and when other measures e.g. demulcents are not effective.
- Use ideal body weight (Appendix 7) when calculating doses in obese children
- In some circumstances, particularly opioid naïve patients at increased risk of adverse effects, it may be appropriate to start at lower doses, between  $\frac{1}{10}$  and  $\frac{1}{2}$  of those quoted above, titrating according to response.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

#### *Cautions*

- Caution in renal or hepatic impairment. Reduce dose and/or interval frequency. Avoid in severe
- renal impairment
- Avoid rectal administration in children with low platelets and/or neutropaenia.

#### *Side effects*

- Usual opioid side effects. Children may have a higher incidence of pruritus and urinary retention
- Toxicity often presents as myoclonic twitching.

#### *Pharmacokinetics*

- Oral absorption more variable and may be higher in neonates
- Orodispersible tablets are dissolved orally and swallowed: no significant buccal or sublingual absorption
- Higher volume of distribution in preterm and neonates especially days 2-5
- Converted to active metabolites by liver then excreted by kidneys: maturation to adult pharmacokinetics by approximately 6 months
- Clearance of morphine in some younger children may be higher than adults
- Some evidence suggests that area under time-concentration curve may be lower for subcutaneous rather than intravenous infusions. However APPM recommendation is to assume similar pharmacokinetics for intravenous and subcutaneous dosing.

#### *Administration*

- Oral solution can be administered undiluted via gastrostomy tube. Dilute with an equal volume of water for administration via a jejunostomy. Flush well to ensure total dose is delivered.
- Zomorph capsules can be opened to release the granules. The granules should not be crushed. Part doses should not be given as accuracy cannot be established. Zomorph granules can mixed with water for administration via an enteral feeding tube. The granules settle quickly in the syringe and care must be taken to deliver the complete dose. Zomorph granules can be administered via a 16Fr and above gastrostomy. Administration tubes as small as 8Fr without blockage has been reported. Caution would be advised in tubes of small diameter and a plan for unblocking the tube should be in place.
- MXL capsules can be opened and sprinkled on to food but are **not** suitable for administration via a feeding tube
- Morphine slow release tablets can be administered rectally.



*Patient information*

- See Medicines for Children leaflet “Morphine for pain”  
<https://www.medicinesforchildren.org.uk/medicines/morphine-for-pain/>

*Available as*

- *Tablets* (10mg-can be halved, 20mg, 50mg). Also available as *orodispersible tablets* (Actimorph®) 1mg, 2.5mg, 5mg, 10mg, 20mg, 30mg. Tablets should be placed on the tongue, and allowed to disperse before swallowing. Alternatively, tablets can be placed in a spoon and dispersed in a small amount of water before administration.
- *Oral solution* 10mg/5ml (Oramorph), concentrated oral solution 100mg/5ml. An unlicensed lower strength oral solution 100micrograms/1ml is available from UK ‘specials’ manufacturers for accurate measurement of small doses especially in neonates.
- *Modified release tablets and capsules* Tablets 12-hourly (5mg, 10mg, 15mg, 30mg, 60mg, 100mg, 200mg), modified release capsules 12-hourly (ZOMORPH 10mg, 30mg, 60mg, 100mg, 200mg), modified release capsules 24-hourly (30mg, 60mg, 90mg, 120mg, 150mg, 200mg).
- *Suppositories* (10mg): other strengths may be available from specials manufacturers.
- *Injection* (1mg/ml, 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml).

*CD*

- CD Schedule 2 except morphine oral solution 10mg/5ml and neonatal morphine solution 100micrograms/ml

## Nabilone

### Use:

- Nausea and vomiting caused by cytotoxic chemotherapy (not first or second line therapy).
- Nausea and vomiting unresponsive to conventional antiemetics.
- Management of upper gastrointestinal symptoms in gut dystonia.

### Dose and route:

By mouth:

- **Child less than 18 kg:** 500micrograms twice daily
- **Child 18- 30 kg:** 1mg twice daily
- **Child over 30 kg:** 1mg three times daily
- **Adult:** 1–2mg twice daily (maximum dose 6mg/day in 2-3 divided doses)

### Notes:

- Synthetic cannabinoid.

#### *Licensing*

- Not licensed for use in children.

#### *Therapeutics*

- Specialist use only. Response varies between patients requiring close medical supervision on commencement and dose adjustments. Effects may persist for a variable and unpredictable period of time following oral administration.

#### *Side effects*

- Somnolence, dizziness and abdominal pain
- Adverse psychiatric reactions can persist for 48-72 hours following cessation of treatment.
- Decreased or increased appetite

#### *Hepatic impairment, renal impairment*

- Avoid in severe hepatic impairment.

#### *Administration*

- No information available regarding administration via enteral feeding tubes

#### *Available as*

- Capsules (250 micrograms, 1mg).

#### *CD*

- Schedule 2 CD.

## Naloxone

### Use:

- Emergency reversal of life threatening opioid-induced respiratory depression or opioid overdose.

### Dose and route:

#### **Partial reversal of respiratory depression due to acute opioid overdose**

When there is risk of acute opioid withdrawal or when a continued therapeutic effect is required

By intravenous injection:

Doses approximately equal to twice the intravenous dose can be given subcutaneously or intramuscularly if intravenous access is not available, but slower onset of action

- **Neonate, child 1 month-11 years:** 1–10micrograms/kg, maximum 200micrograms per dose

Then, if no response, repeat at intervals of 1 minute up to 5 times

Then, if still no response, single dose of 100micrograms/kg (maximum dose 2mg)

- **12 years and over:** 100–200micrograms per dose

Then, if no response, 100micrograms at 1 minute intervals for up to 2 doses

Then, if still no response continue titrating up to a maximum of 2mg per dose

- If still no response, give a further 2mg dose: 4mg dose may be required in seriously compromised patients

Review diagnosis if still no response. Further doses, or infusion, may be required if respiratory function deteriorates following initial response.

By continuous intravenous infusion

Continued partial reversal of respiratory depression due to acute opioid overdose e.g. for long acting opioids

- 60% of the initial effective dose per hour, rate adjusted according to response

Initial effective dose is that which maintained satisfactory self-ventilation for 15 minutes.

#### **Complete reversal of respiratory depression due to acute opioid overdose**

By intravenous injection:

Doses approximately equal to twice the intravenous dose can be given subcutaneously or intramuscularly if intravenous access is not available, but slower onset of action

- **Neonate, child 1 month-11 years:** 100micrograms/kg.  
Then, if no response repeat at intervals of 1 minute to a maximum of 2mg
  - **12 years and over:** initially 400micrograms.  
Then, if no response, 800micrograms at 1 minute intervals for up to 2 doses  
Then, if still no response, 2mg for 1 dose: 4mg dose may be required in seriously compromised patients.
- Further doses, or infusion, may be required if respiratory depression deteriorates following initial response

By intranasal route

- **Child body-weight 9kg and over:** 1.8 mg, administered into one nostril  
Repeat dose into alternate nostril if no response after 2-3 minutes.  
Repeat dose immediately if initial response is followed by further respiratory depression. Administer into alternate nostrils.

By continuous intravenous infusion

Continued complete reversal of respiratory depression due to acute opioid overdose e.g. for long acting opioids

- 60% of the initial resuscitative dose per hour, rate adjusted according to response  
Initial resuscitative dose is that which maintained satisfactory self-ventilation for 15 minutes.

## Notes

- Potent opioid antagonist.

### *Licensing*

- Intranasal spray not licensed for children below 14 years; limited experience in children.

### *Therapeutics*

- In some circumstances temporary discontinuation of strong opioids together with close observation may be sufficient, rather than proceeding immediately to opioid reversal
- May have a role in reversal of clonidine toxicity.

### *Side effects*

- Arrhythmias, dizziness, headache, hypertension, hypotension, nausea and vomiting.

### *Pharmacokinetics*

- Short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.
- Naloxone acts within 2 minutes of IV injection and within 3-5 minutes of SC or IM injection.
- Intranasal bioavailability approximately 50% *depending on formulation*

### *Available as*

- Injection (20micrograms/ml, 400micrograms/ml, 21mg/2ml) and nasal spray 1.8m/0.1ml.

## Naproxen

### Use:

- Non-steroidal anti-inflammatory analgesic
- Relief of symptoms in inflammatory arthritis and treatment of acute musculoskeletal syndromes

### Dose and route:

By mouth

- **Child 2 years and over:** 5-7.5mg/kg/dose twice daily (maximum 1g/ day)

Doses up to 10mg/kg twice daily (not exceeding 1g daily) have been used. Use the lowest effective dose for the shortest treatment duration possible.

### Notes:

#### *Licensing*

- 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.

#### *Therapeutics*

- Generally regarded as combining good efficacy with a low incidence of side effects.
- Anti-pyretic and anti-inflammatory actions may reduce fever and inflammation therefore reducing their utility as diagnostic signs.

#### *Contraindications, cautions*

- Contraindicated in patients with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

#### *Side effects*

- All NSAID use can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.
- All NSAIDs are associated with serious gastro-intestinal toxicity. Naproxen is associated with an intermediate risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.

#### *Hepatic impairment, renal impairment*

- 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 in GFR <20ml/min/1.73m<sup>2</sup> and in those with severe hepatic or cardiac failure.

*Administration*

- For administration via an enteral feeding tube, using the oral suspension or effervescent tablets. 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 250mg and 500mg; effervescent tablets 250mg; enteric coated tablets 250mg, 375mg and 500mg; oral suspension 125mg/5ml, 25mg/ml, 50mg/ml.

## Nitrous oxide (Entonox®)

### Use:

- As self-regulated analgesia without loss of consciousness e.g. painful dressing changes
- Not suitable for use outside of an acute healthcare setting

### Dose and route:

By inhalation:

- **Child 2 years and over:** Up to 50% to be administered using suitable anaesthetic apparatus in oxygen adjusted according to the patient's needs. Self-regulated use usually over 5 years of age.

### Notes:

#### *Therapeutics*

- Normally used as a light anaesthetic. Rapid onset and then offset.
- Training, governance and supply implications may limit application in hospice settings.

#### *Contraindications, cautions*

- Contraindicated in the presence of pneumothorax or intracranial air after head injury.

#### *Side effects*

- Risk of hypoxia immediately after administration: administer supplementary oxygen for several minutes following administration.
- Prolonged exposure (including environmental exposure to relatives) by continuous or intermittent administration may result in megaloblastic anaemia. Consider assessment of plasma vitamin B12 concentration. Depression of white cell formation may also occur. Neurological toxicity may occur without preceding overt haematological changes.
- Consider assessment of plasma vitamin B12 concentration in children at risk of deficiency.

#### *Interactions*

- Avoid concomitant use with methotrexate: increased antifolate effect.
- Risk of enhanced hypotensive effect with a number of medications.

#### *Administration*

- Should only be used as self-administration using a demand valve; all other situations require a specialist paediatric anaesthetist.

#### *Patient information*

- See Medicines for Children leaflet "Nitrous oxide for pain"  
<https://www.medicinesforchildren.org.uk/medicines/nitrous-oxide-for-pain/>

#### *Available as*

- Nitrous oxide 1ml per 1ml various sizes of cylinders available from medical gas suppliers Linde Gas UK and BOC Ltd. See BNFC for additional information.



## Nystatin

### Use:

- Oral and perioral fungal infection.

### Dose and route:

By mouth:

- **Neonate:** 100,000 units 4 times daily
- **Child 1-23 months:** 100,000-200,000 units 4 times daily
- **2 years and over:** 100,000-600,000 units 4 times daily

### Notes:

#### *Licensing*

- Licensed for use in all ages. Licensed for prophylaxis against oral candidiasis in neonates at a dose of 1ml daily.

#### *Therapeutics*

- Treatment for 7 days and should be continued for 48 hours after lesions have healed.
- Higher doses allow greater mucosal contact and may therefore be more effective.

#### *Administration*

- Retain near lesions before swallowing.

#### *Side effects*

- Abdominal discomfort; angioedema; diarrhoea; facial oedema; nausea; sensitisation; skin reactions; Stevens-Johnson syndrome; vomiting
- Administer after food or feeds. If possible divide the dose between both sides of the mouth.

#### *Available as*

- Oral suspension 100,000 units/ml, 30ml with pipette.

## Octreotide

### Use:

- Bleeding from oesophageal or gastric varices.
- Nausea and vomiting.
- Inoperable intestinal obstruction.
- Intractable diarrhoea.
- Hormone secreting tumours, ascites, bronchorrhoea.
- Chylothorax
- Hyperinsulaemic hypoglycaemia (specialist use)

### Dose and route:

#### Gastrointestinal bleeding, chylothorax (NEW)

By continuous intravenous or subcutaneous infusion

- **Child 1 month and over:** 1microgram/kg/hour

Higher doses may be required initially and for chylothorax. Usual maximum dose is 50micrograms/hour

Reduce dose gradually over 24hours once there is no active bleeding.

#### Antiemetic, antisecretory, intractable diarrhoea, intestinal obstruction

By continuous intravenous or subcutaneous infusion

- **Child 1 month and over:** 5-10micrograms/kg/24hours. Usual maximum 750micrograms/24hours

Doses up to 30micrograms/kg/24hours may be required in intractable diarrhoea.

#### Hyperinsulaemic hypoglycaemia unresponsive to diazoxide and glucose (specialist use) (NEW)

By subcutaneous injection

- **Neonate:** Initially 2–5micrograms/kg every 6–8 hours, adjusted according to response; increased if necessary up to 7micrograms/kg every 4 hours, dosing up to 7micrograms/kg may rarely be required.
- **Child 1 month and over:** Initially 1–2micrograms/kg every 4–6 hours, adjusted according to response; increased if necessary up to 7micrograms/kg every 4 hours, dosing up to 7micrograms/kg may rarely be required.

**Notes:**

- Synthetic somatostatin analogue

*Licensing*

- Not licensed for use in children.

*Therapeutics*

- Acts as an inhibitory hormone throughout the body but particularly the gastro-enterohepatic system, increasing water and electrolyte absorption.
- Avoid abrupt withdrawal: may be associated with biliary colic and pancreatitis.
- May impair glucose tolerance: consider monitoring blood glucose.
- Rotate injection sites

*Administration*

- Dilute with sodium chloride 0.9% for intravenous injection and intravenous or subcutaneous infusion. Check the manufacturer's recommendations regarding dilution. Subcutaneous bolus injections may be administered undiluted but this can be painful (this can be reduced if the ampoule is warmed in the hand to body temperature before injection).

*Available as*

- Injection for subcutaneous or intravenous administration (50micrograms/ml, 100micrograms/ml, 200micrograms/ml, 500micrograms/ml, 1mg/5ml). Also available as depot injection for intramuscular administration every 28 days (10mg, 20mg and 30mg SandostatinLar®).

## Olanzapine

### Use:

- Psychoses; delirium; agitation; anorexia when all other treatments have failed.
- Nausea and vomiting.

### Dose and route:

#### Psychoses, mania

By mouth

- **Child under 12 years and up to 25kg:** Initial dose 2.5mg at night
- **Child under 12 years and greater than 25kg:** Initial dose 2.5-5mg at night.
- **12 years and over:** initial dose 5mg at night.

Increase gradually as necessary and as tolerated to a maximum of 20mg/day given usually as a single dose at night. Can be given as twice daily dose if needed.

#### Agitation, delirium

By mouth

- **Child under 12 years:** Initial dose 1.25mg at night and as required,
- **12 years and over:** Initial dose 2.5mg at night and as required.

Increase gradually as necessary and as tolerated to maximum 10mg/day

#### Nausea and vomiting, anorexia

- **Child under 12 years:** Initial dose 1.25mg (or 625micrograms if 2.5mg tablets can be cut into quarters) at night and as required
- **12 years and over:** Initial dose 1.25mg-2.5mg at night and as required.

Dose may be increased as necessary and as tolerated to a suggested maximum of 7.5mg/day.

### Notes:

- Atypical (second generation) antipsychotic agent and antagonist of dopamine D1, D2, D4, 5-HT<sub>2</sub>, histamine-1-, and muscarinic-receptors.

*Licensing*

- 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.

#### *Therapeutics*

- Five times greater affinity for 5HT<sub>2</sub> receptors than for D<sub>2</sub> receptors, resulting in fewer extrapyramidal side effects.
- Activity at multiple receptors is similar to levomepromazine.
- Titrate dose slowly to minimise sedation.
- Adolescents may be more susceptible to weight gain
- Elevated lipid and prolactin levels. Consider monitoring before and during long term use
- Onset of action is hours-days in delirium; days-weeks in psychoses.

#### *Contraindications, cautions*

- Caution in cardiovascular disease. Caution in epilepsy and conditions predisposing to seizures: lowers seizure threshold

#### *Side effects*

- Very common (> 10% patients) side 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) side 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 and hyperglycaemia.

#### *Hepatic impairment, renal impairment*

- Consider lower starting dose (maximum 5mg in adults) in patients with renal and/or hepatic impairment.

#### *Interactions*

- Metabolised by CYP1A2. Pharmacokinetics may be affected by co-administration of other substances using this isoenzyme e.g. carbamazepine, fluvoxamine, nicotine.

#### *Administration*

- Orodispersible tablets can be dissolved in a drink immediately before oral administration.
- Orodispersible tablets can be dissolved in water for administration via feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy. Anecdotal reports that 5mg orodispersible tablets may be halved to give a 2.5mg dose: halve immediately before administration and discard the remaining portion.
- 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.

#### *Patient information*

- Patient information see Medicines for Children leaflet "Olanzapine for schizophrenia bipolar disorder mania and agitation"  
<https://www.medicinesforchildren.org.uk/medicines/olanzapine-for-schizophrenia-bipolar-disorder-mania-and-agitation/>

#### *Available as*

- Tablets 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg; orodispersible tablets / lyophilisate, 5mg, 10mg, 15mg, 20mg.

## Omeprazole

### Use:

- Gastro-oesophageal reflux.
- Acid related dyspepsia.
- Gastrointestinal prophylaxis (e.g. with NSAID or steroids).
- Treatment of duodenal and gastric ulcers.

### Dose and route:

By mouth:

- **Neonate:** 700micrograms/kg once daily; increase if necessary to a maximum of 1.4mg/kg-2.8mg/kg once daily
- **Child 1 month-1 year:** 700micrograms/kg once daily; increase if necessary to a maximum of 3mg/kg or 20mg once daily
- **Child 10-19 kg:** 10mg once daily, increase if necessary to a maximum of 20mg once daily
- **20 kg and above:** 20mg once daily, increase if necessary to a maximum of 40mg once daily.

By intravenous infusion (over 20-30 minutes)

- **Child 1 month-11 years:** initially 500micrograms/kg, maximum 20mg/dose, once daily. Increase if necessary, to 2mg/kg, maximum 40mg/dose, once daily.
- **12 years and over:** 40mg once daily.

### Notes:

- Proton pump inhibitor

#### *Licensing*

- 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 12years.

#### *Therapeutics*

- Many children with life limiting conditions have gastro-oesophageal reflux disease and may need to continue with treatment long term.

#### *Side effects*

- May cause agitation. Occasionally associated with electrolyte disturbance.
- MHRA safety warning 2015: very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs.
- Constipation, diarrhoea, vomiting

*Interactions*

- Inhibits cytochrome P450 enzyme CYP2C19. May increase levels of drugs metabolised by this enzyme including diazepam.
- Metabolised by CYP2C19 and CYP3A4. Levels may increased by drugs that inhibit these enzymes including fluconazole.

*Administration*

- For oral administration tablets can be dispersed in water or mixed 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. Omeprazole is absorbed when administered into the jejunum with no reduction in bioavailability. Choice of formulation depends on the size of tube.
- Intermittent subcutaneous administration has been reported at doses equivalent to the intravenous route, diluted to a concentration of 400micrograms/ml in sodium chloride 0.9%

*Patient information*

- Patient information see Medicines for Children leaflet “Omeprazole for gastro-oesophageal reflux disease (GORD)”  
<https://www.medicinesforchildren.org.uk/medicines/omeprazole-for-gastro-oesophageal-reflux-disease-gord/>

*Available as*

- Gastroresistant tablets (MUPS) tablets (10mg, 20mg, 40mg), capsules (10mg, 20mg, 40mg), intravenous infusion (40mg). Oral suspensions of strengths 10mg/5ml and 20mg/5ml are now available as licensed products in the UK. Other formulations of unlicensed oral suspensions are currently still available from UK ‘specials’ manufacturers.

## Ondansetron

### Use:

- Antiemetic, particularly in vomiting caused by damage to gastrointestinal mucosa (e.g. chemotherapy or radiotherapy, severe gastroenteritis)
- Adjunct to levomepromazine in severe nausea and vomiting
- Opioid induced pruritus

### Dose and route:

#### Prevention and treatment of chemotherapy and radiotherapy-induced nausea and vomiting

By intravenous infusion over at least 15 minutes

- **Child 6 months and over:** 5mg/m<sup>2</sup> or 150micrograms/kg immediately before chemotherapy maximum 8mg/dose.

Dose can be repeated every 4 hours for 2 further doses before changing to oral route. Alternatively change to oral route after initial intravenous dose. Maximum total daily dose 32mg by any route

By mouth following intravenous administration

Oral dosing can start 12 hours after intravenous administration

- **Child 6 months and over:**

**Surface area less than 0.6m<sup>2</sup> or less than 10kg:** 2mg every 12 hours for up to 5 days, maximum total daily dose 32mg

**Surface area 0.6m<sup>2</sup>-1.2m<sup>2</sup> or 10- 40kg:** 4mg every 12 hours for up to 5 days, maximum total daily dose 32mg

**Surface area over 1.2m<sup>2</sup> or over 40kg:** 8mg every 12 hours for up to 5 days, maximum total daily dose 32mg

#### Nausea and vomiting, pruritus

By mouth or slow intravenous injection over 2-5 minutes or by intravenous infusion over 15 minutes

- **Child 6 months and over:** 100-150micrograms/kg/dose every 8 -12 hours, maximum 8mg/dose

### Notes:

- Serotonin (5HT<sub>3</sub>) receptor antagonist

#### *Licensing*



- Injection licensed for the management of chemotherapy-induced nausea and vomiting in children over 6 months, and for the prevention and treatment of post-operative nausea and vomiting in children (as a single dose) from 1 month. Oral ondansetron licensed from 6 months of age for the management of chemotherapy-induced nausea and vomiting. Oral formulation not recommended for post-operative nausea and vomiting in children due to a lack of data. Injection is not licensed for subcutaneous administration.

#### *Therapeutics*

- Pure 5HT<sub>3</sub> antagonist, so receptor profile is complementary to levomepromazine. Consider for nausea and vomiting not controlled by regular levomepromazine.

#### *Contraindications, cautions*

- Contraindicated in patients with congenital long QT syndrome
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, electrolyte imbalance or taking other drugs known to prolong the QT-interval

#### *Side effects*

- Powerfully constipating. Headache is a common adverse effect
- Possible side effects include nausea, vomiting, sweating and intestinal colic

#### *Pharmacokinetics*

- Decreased clearance in neonates (75%) in neonates and infants (50% at 3 months). Monitor closely if administered to children under 6 months. Consider increasing dosing interval and reducing dose.
- Onset of action oral less than 30 minutes, intravenous less than 5 minutes and duration 12 hours

#### *Administration*

- Orodispersible films should be placed on the tongue and allowed to disperse before swallowing. NB absorption of active drug does NOT occur via the oral mucosa, it is dependent on the dispersed tablet being swallowed
- For intravenous infusion, dilute to a concentration of 320–640micrograms/ml with dextrose 5% or sodium chloride 0.9% or Ringer's solution; give over at least 15 minutes.
- Oral solution contains sorbitol.
- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Case reports of administration by continuous subcutaneous infusion, diluted in sodium chloride 0.9% at concentrations of between 100micrograms/ml and 2mg/ml. Ondansetron injection has a low (acidic) pH and the formulation may cause localised site reactions particularly at higher concentrations.

#### *Available as*

- Tablets (4mg, 8mg, orodispersible films/tablets (4mg, 8mg), oral solution (4mg/5ml, 8mg/5ml), injection (2mg/ml, 2ml and 4ml amps).

## Oxybutynin

### Use:

- Neurogenic or overactive bladder
- Symptomatic treatment of urinary incontinence, urgency and frequency in the unstable bladder whether due to neurogenic bladder disorders or idiopathic detrusor instability

### Dose and route:

By mouth

Using immediate release preparation

- **Child up to 2 years:** 100-200micrograms/kg/dose 2-3 times daily. Maximum 12.5mg/dose
- **2-4 years:** 1.25-2.5mg/dose 2-3 times daily
- **5-11 years:** initial dose 2.5-3mg/dose twice daily, increasing to 5mg 2-3 times daily if needed
- **12 years and over:** initial dose 5mg/dose 2-3 times daily, increasing up to 5mg 4 times daily if needed

Using modified-release preparation

- **Child 5 years and over:** 5mg once daily adjusted, according to response, in increments of 5mg every week to a maximum of 15mg daily

Transdermal

Using Kentera® matrix patch

*Approximate* equivalent doses (see also notes below)

Oral oxybutynin 2.5–5mg/24hours	≡	¼ patch (1.3mg/24hours) twice weekly
Oral oxybutynin 5-10mg/24hours	≡	½ patch (2.6mg/24hours) twice weekly
Oral oxybutynin 10-15mg/24hours	≡	1 patch (3.9mg/24hours) twice weekly

Intravesical

- **Child 2 years and over:** 5mg 2-3 times daily

## Notes:

- Antispasmodic with direct effect on smooth muscle and also inhibits the action of acetylcholine on smooth muscle. Increases bladder capacity, decreases uninhibited contractions and delays desire to void therefore decreasing urgency and frequency

### *Licensing*

- Oral oxybutynin is not licensed for use in children less than 5 years of age. Intravesical and transdermal routes are not licensed in children. Intravesical formulation is unlicensed. Cutting patches is outside product licence

### *Therapeutics*

- Transdermal administration of oxybutynin substantially bypasses the extensive first-pass metabolism that occurs with oral administration, reducing the formation of N-desethyloxybutynin (reducing systemic exposure to the active metabolites with a suggested reduction in incidence of adverse effects)
- An exact pharmacodynamic comparison between immediate release oxybutynin and transdermal oxybutynin is not possible due to their metabolic profiles being very different. There is no study of the therapeutic equivalence of immediate release oxybutynin and transdermal oxybutynin. The suggested starting point in dosing is derived from past efficacy response and is not exact because disease syndrome, patient response and acceptability is very diverse and unpredictable. Individual patient titration upwards or downwards is warranted to obtain the best therapeutic response.

### *Contraindications, cautions*

- Contraindicated in myasthenia gravis, glaucoma, gastrointestinal obstructive disorders including paralytic ileus or intestinal atony, toxic megacolon, severe ulcerative colitis, bladder outflow obstruction
- Young children may be more sensitive to the adverse effects of oxybutynin, particularly the CNS and psychiatric adverse reactions.

### *Adverse Effects*

- Common adverse effects due to antimuscarinic properties include: confusion, constipation, dizziness, drowsiness, dry mouth, dyspepsia, flushing, headache, nausea and vomiting, palpitations, tachycardia, blurred vision. Oral solutions containing sorbitol may cause diarrhoea

### *Renal Impairment and hepatic impairment*

- Use with caution due to limited experience. Possible increased risk of adverse effects

### *Pharmacokinetics*

- Transdermal: following application of the patch, oxybutynin plasma concentration increases for ~24-48 hours; steady state concentrations are reached during application of the second patch. Thereafter, steady concentrations are maintained for up to 96 hours

### *Interactions*

- Increased risk of anticholinergic side effects with concurrent use of other anticholinergics
- By reducing gastric motility, oxybutynin may affect the absorption of other drugs and antagonise the effect of prokinetic medication

*Administration*

- Tablets should be swallowed whole to avoid unpleasant taste
- Apply patches should be applied to dry, intact skin on the abdomen, hip or buttock immediately after removal from the protective sachet. A new application site should be used with each new patch (do not reapply to same site within 7 days).
- Patches can be cut without affecting the mechanism, rate or amount of oxybutynin released. Transdermal patch may contain metal-remove patch prior to MRI
- Intravesical-after emptying the bladder, administer intravesical solution directly into the bladder via a catheter
- Use liquid formulation for administration via a feeding tube. Alternatively immediate release tablets may be crushed immediately prior to administration. Oxybutynin immediate release tablets may be crushed and mixed with water for administration via an enteral feeding tube. Flush well after administration. No specific data for jejunal administration: suggest administration as for gastrostomy, using liquid preparation, and monitor for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children Leaflet "Oxybutynin for daytime urinary symptoms"  
<https://www.medicinesforchildren.org.uk/medicines/oxybutynin-for-daytime-urinary-symptoms/>

*Available as*

- Immediate release tablets: 2.5mg, 3mg, 5mg. Modified-release tablets: 5mg, 10mg. Oral solution: 2.5mg in 5ml, 5mg in 5ml. Intravesical solution is available as an unlicensed special. Transdermal patches: patches contain 36mg of oxybutynin and release 3.9mg oxybutynin per 24 hours (Kentera®)

## Oxycodone

### Use:

- Alternative opioid analgesic for severe pain

Important safety information

#### For all opioids

#### MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The **APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### Pain in patients already receiving regular strong opioids

Convert using oral morphine equivalent (OME) from previous opioid analgesia, if applicable, see Appendix 1

By mouth using immediate release preparations

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Oxycodone oral	2:1	Divide morphine oral dose by 2	Morphine oral 20mg ÷ 2 = oxycodone oral 10mg

Consider reducing the dose of oxycodone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

By mouth using modified release preparations

- Use oral morphine equivalent (as above) to convert current doses of previous opioid analgesia, if applicable, *then*
- Calculate the total daily dose (regular + PRN) of oral oxycodone administered over the previous 24 hours once the patient is established on regular strong opioid analgesia for 2-3 days

*12 hourly preparations:* Divide the total daily dose of oral oxycodone by two and administer every 12 hours

*24 hourly preparations:* Administer the total daily dose of oral oxycodone every 24 hours

Ensure continued access to immediate release oxycodone as required for breakthrough pain see below

By single intravenous or subcutaneous bolus injection

Conversion		Ratio	Calculation	Example
From	To			
Oxycodone oral single dose	Oxycodone SC or IV bolus single dose	1.5:1	Divide oxycodone oral dose by 1.5	Oxycodone oral 4.5mg ÷ 1.5 = Oxycodone IV/SC <i>bolus</i> 3mg

Consider reducing the dose of oxycodone by  $\frac{1}{4}$ - $\frac{1}{2}$  when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

By continuous intravenous or subcutaneous infusion

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Oxycodone CSCI or CIVI	3:1	Divide 24hour morphine dose by 3	Morphine oral 60mg/24hour ÷ 3 = oxycodone CSCI 20mg/24hours
Oxycodone oral	Oxycodone CSCI or CIVI	1:5:1	Divide 24hour dose of oral oxycodone by 1.5	Oxycodone oral 90mg/24hours ÷ 1.5 = oxycodone CSCI 60mg/24hours
Morphine CSCI or CIVI	Oxycodone CSCI or CIVI	1:1	Use the same dose	Morphine CSCI 50mg/24h = oxycodone CSCI 50mg/24hours

Consider reducing the dose of oxycodone by  $\frac{1}{4}$ - $\frac{1}{2}$  when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

### Breakthrough pain in patients already receiving opioids

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10-1/6 of total daily oxycodone dose every 4-6 hours as required.

Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

### Pain in opioid naïve patients

Opioid naïve patients: the maximum dose stated applies to starting dose only

By mouth using immediate release preparations:

- **Child 1 month-11 years**<sup>28</sup>: Initial dose 100micrograms/kg, maximum single dose 5mg, every 4 -6 hours, increase as necessary according to severity of pain.
- **12 years and over**: Initial dose 5mg every 4-6 hours, increase as necessary according to severity of pain.

### Notes:

- Opioid analgesic with similar efficacy and side effects to morphine. Generally, only appropriate for patients intolerant of morphine.

#### *Licensing*

- Not licensed for use in children less than 12 years of age. Available in combination with naloxone as alternative to laxative therapy in opioid-induced constipation Targinact® (Napp) not licensed in children.

#### *Therapeutics*

- Like morphine, oxycodone is primarily a Mu opioid receptor agonist. However, differences in structure mean that it may be effective for opioid substitution
- No neonatal dose available
- Reason behind odd conversion ratio is bioavailability and rounding factors for safety
- Strong oral solution has been used sublingually in adults
- Injection solution has been administered in children via sublingual and buccal routes. Doses equivalent to those given by mouth appear to be effective with similar onset of action and bioavailability: it is unclear how much of the drug is being absorbed via the transmucosal route and how much is being swallowed.
- Modified release preparations have also been administered via the rectal route

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<sup>28</sup> Dose modified from BNFC taking into account APPM recommendations for morphine and equianalgesia

- Oral bioavailability may be lower in younger children and infants
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

*Cautions*

- Caution in hepatic or renal impairment.

*Side effects*

- Usual opioid side effects

*Interactions*

- Metabolised by cytochrome P450 enzymes CYP2D6 and CYP3A4. Levels increased by drugs that inhibit these enzymes including celecoxib, ciprofloxacin, erythromycin and fluconazole. Levels reduced by drugs that induce these enzymes including carbamazepine and phenobarbital.

*Administration*

- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with water for injection, 0.9% sodium chloride or 5% dextrose.
- Oxycodone liquid may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Modified release tablets are available as 12-hourly and 24-hourly preparations. Care with prescribing and do not confuse brands.

*Available as*

- Capsules (5mg, 10mg, 20mg), tablets (5mg),
- Oral solution (5mg/5 ml, 10mg/ml)
- Modified release tablets **12-hourly** (5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg, 120mg),
- Modified-release tablets **24-hourly** (10mg, 20mg, 40mg, 80mg)
- Injection (10mg/ml and 50mg/ml).

*CD*

- CD Schedule 2



## Oxygen

### Use

- Breathlessness caused by hypoxaemia
- Pulmonary Hypertension
- Placebo effect for dyspnoea, especially where family feels need to intervene promptly
- Alternative to air blowing on face

### Dose and route:

By inhalation through nasal cannula

- Flow rates of 1– 2.5L/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:

#### *Therapeutics*

- No convincing evidence for O<sub>2</sub> in non-hypoxemic patients: moving air from a fan may be equally effective. Nevertheless, some patients do appear to benefit: try it and if it doesn't help stop.
- Oxygen has little effect in raising SaO<sub>2</sub> in cyanotic congenital heart disease and is not generally indicated. Pulmonary hypertension, in the early stages, may respond to oxygen.

#### *Monitoring*

- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Observation of the work of breathing is a more reliable indicator of breathlessness where self-report is not possible.
- Decisions regarding target oxygen saturations and monitoring should be guided by the overall aims of oxygen treatment and realistic saturation levels for an individual child.
- 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.
- Usual target oxygen saturations of 92-96% 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.

#### *Side effects*

- Continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.

*Administration*

- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions.
- 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 daily.
- If necessary, two concentrators can be Y-connected to supply very high oxygen concentrations.
- Liquid oxygen is more expensive but provides a longer duration of portable oxygen supply. Portable oxygen concentrators are now also available.
- Higher concentrations of oxygen are required during air travel.

*Available as*

- Currently Air Liquide ([www.airliquidehealthcare.co.uk](http://www.airliquidehealthcare.co.uk)) and Dolby Vivisol ([www.dolbyvivisol.com](http://www.dolbyvivisol.com)) provide home oxygen to the UK.

## Pamidronate (Disodium)

### Use:

- Adjuvant for bone pain caused by metastatic disease.
- Adjuvant for bone pain due to osteopenia or osteoporosis associated with neuromuscular conditions.
- Malignant hypercalcaemia.
- Treatment of secondary osteoporosis to reduce fracture risk.
- Osteogenesis imperfecta.

### Dose and route:

#### Malignant hypercalcaemia

By intravenous infusion:

- **Child less than 2 years:** 500microgram/kg/dose
- **2- 3 years:** 750microgram/kg/dose
- **3 years and over:** 1mg/kg/dose, maximum 90mg/dose

Ensure adequate rehydration with intravenous sodium chloride 0.9%. Dilute pamidronate to a concentration of no more than 90mg/250ml sodium chloride 0.9% and infuse over 6 hours

Repeat up to weekly, as indicated by corrected serum calcium

#### Bone pain, metastatic bone disease, osteopenia, osteoporosis, osteogenesis imperfecta

By intravenous infusion:

Seek specialist advice

Age	Dose per infusion	Infusions per cycle	Repeat cycle	Alternative regimes
<b>Child less than 2 years</b>	500microgram/kg/dose	1 infusion daily for 3 consecutive days	Every 2 months	Can also be given as 750microgram/kg/infusion for 2 consecutive days every 2 months
<b>Child 2- 3 years</b>	750microgram/kg/dose	1 infusion daily for 3 consecutive days	Every 3 months	The same dose per infusion can also be given once every month

<b>Over 3 years</b>	1mg/kg/dose maximum 60mg/dose	1 infusion daily for 3 consecutive days	Every 3 months	OR the same dose per infusion can be given on 2 consecutive days every 2 months
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Dilute pamidronate to a concentration of no more than 90mg/250ml 0.9% sodium chloride and infuse over 6 hours

## Notes:

### *Licensing*

- Not licensed for use in children. Not licensed for osteogenesis imperfecta.

### *Therapeutics*

- Regimes vary between centres. Choice of regime depends on local guidelines and convenience. Some centres advise DEXA scan and investigations into calcium metabolism before and after treatment.
- Response to treatment of osteopenia or osteoporosis, and indications for on-going treatment, should be assessed after 1- 2 years treatment.
- Effectiveness of Pamidronate in bone pain does not necessarily depend on demonstrating osteoporosis, but demonstration that iatrogenic osteopetrosis has not developed afterwards can be reassuring.
- Pain may initially increase before improving.
- Improvement in bone pain may occur within two weeks in osteopenia or osteoporosis. However improvement in bone density may not be apparent for up to a year.
- 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).
- Other 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. Seek specialist advice.
- Denosumab is considered second line for refractory malignant hypercalcaemia

### *Caution*

- Monitor renal function and electrolytes; ensure adequate hydration. Risk of renal impairment is increased by concurrent use with other nephrotoxic drugs

### *Interactions*

- Prolonged hypocalcaemia and hypomagnesaemia may occur with concurrent use of aminoglycoside and a bisphosphonate.

### *Side effects*

- Tolerated by children, but long term effects unknown.
- Flu-like symptoms are common with first infusion, but don't necessarily recur with subsequent doses.
- Atypical femoral fractures, and of osteonecrosis especially of the jaw and the external auditory canal reported in adults. Risk in children is uncertain. Consider dental review before treatment, attention to dental hygiene together with patient and / or family education.

### *Administration*

- Initial dose is usually given as an inpatient. Subsequent doses could be given at home if necessary medical and nursing support is available.
- Can be administered by continuous subcutaneous infusion over 12-24 hours, together with subcutaneous hydration.

*Available as*

- Injection vials for infusion of various volumes, at 3mg/ml, 6mg/ml, 9mg/ml, 15mg/ml.

## Paracetamol

(US: Acetaminophen)

### Use:

- Mild to moderate pain
- Pyrexia.

### Dose and route:

#### Important safety information

MHRA advice: Paracetamol: updated dosing for children to be introduced (December 2014)

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 75-150mg/kg/day.

APPM recommends body-weight-based dosing where possible because

- Many patients have lower than average body-weight for age
- Patients are more likely to be receiving paracetamol regularly
- Patients are more likely to be receiving enzyme inducing medication e.g. antiepileptics
- Patients are more likely to be at risk of hepatic and or renal impairment

By mouth:

Body-weight-based dosing: recommended

*Warn parents or carers that doses may be different to "usual" doses stated on over the counter medication.*

- **Neonate 28-32 weeks corrected gestational age:** 20mg/kg as a single dose then 10-15mg/kg every 8-12 hours as necessary, maximum 30mg/kg/day in divided doses
- **Neonate over 32 weeks corrected gestational age:** 20mg/kg as a single dose then 10-15mg/kg every 6-8 hours as necessary maximum 60mg/kg/day in divided doses
- **Child 1 month- 5 years:** 20-30mg/kg as a single dose then 15-20mg/kg every 4-6 hours as necessary, maximum 75mg/kg/day in divided doses
- **Child 6-11 years:** 20-30mg/kg, maximum 1 g, as a single dose then 15-20mg/kg every 4-6 hours as necessary, maximum 75mg/kg/day or 4 g/day in divided doses
- **Over 12 years:** 15-20mg/kg, maximum 500mg-1 g, every 4-6 hours as necessary, maximum 4 g/day in divided doses.

By rectum:

Body-weight-based dosing: recommended

- **Neonate 28- 32 weeks corrected gestational age:** 20mg/kg as a single dose then 10-15mg/kg every 12 hours as necessary, maximum 30mg/kg/day in divided doses.
- **Neonates over 32 weeks corrected gestational age:** 30mg/kg as a single dose then 15-20mg/kg every 8 hours as necessary, maximum 60mg/kg/day in divided doses.
- **Child 1- 2 months:** 30mg/kg as a single dose, then 15-20mg/kg every 4-6 hours as necessary, maximum 75mg/kg/day in divided doses.
- **3 months-11years:** 30mg/kg as a single dose, maximum 1 g, then 15-20mg/kg every 4-6 hours as necessary, maximum 75mg/kg/day or 4 g/day in divided doses
- **Over 12 years:** 15-20mg/kg, maximum 500mg -1 g, every 4-6 hours as necessary, maximum 4 g/day in divided doses.

By intravenous infusion over 15 minutes

- **Preterm neonate less than 32 week corrected gestational age:** 7.5mg/kg every 12 hours
- **Preterm neonate over 32 weeks corrected gestational age:** 7.5mg/kg every 8 hours
- **Neonate:** 10mg/kg every 4-6 hours, maximum 30mg/kg/day
- **Infant and child body-weight less than 10 kg:** 10mg/kg every 4-6 hours, maximum 30mg/kg/day
- **Child body-weight 10-50 kg:** 15mg/kg every 4-6 hours, maximum 60mg/kg/day
- **Body-weight over 50 kg:** 1g every 4-6 hours, maximum 4g/day

## Notes:

### *Licensing*

- 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 500mg/5 ml not licensed for use in children under 16 years. IV infusion dose not licensed in children and neonates under 10kg.
- 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.
- Intravenous paracetamol is licensed for short term treatment of moderate pain, and of fever when other routes are not available.

### *Therapeutics*

- Consider use of non-pharmacological measures to relieve pain, as alternative or in addition to analgesics.
- For management of feverish illness in children, see updated NICE clinical Guideline NG143. (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. Do not use antipyretic agents with the sole aim of reducing body temperature). 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”.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

### *Contraindications, cautions*

- Caution in duct dependent congenital heart disease. Administration may stimulate duct closure. Seek specialist cardiology advice.

### *Hepatic impairment, renal impairment*

- Increase dosing interval to 6 hours in moderate renal impairment. Increase dosing interval to 8 hours in severe renal impairment.

### *Pharmacokinetics*

- Onset of action 15-30 minutes by mouth. Onset of action 5-10 minutes IV for analgesia and 30 minutes IV as an antipyretic.
- May take up to 2 hours for full effects. Duration of action 4-6 hours orally and IV.
- Oral bioavailability 60-90%. Rectal bioavailability about 2/3 of oral. Rectal absorption is slower than oral, erratic and incomplete.
- Elimination is slower in babies under 3 months.

### *Side effects*

- Hepatotoxic in overdose (more than 75mg/kg) or prolonged high doses.

### *Administration*

- Oral preparation can be administered rectally and is absorbed more quickly than suppositories.
- Dispersible tablets have high sodium content (over 14mmol per tablet). Consider liquid preparation for regular administration
- 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 intra-jejunally, dilute with at least an equal quantity of water to reduce osmolarity and viscosity.

### *Patient information*

- See Medicines for Children leaflet “paracetamol for mild to moderate pain”:  
<https://www.medicinesforchildren.org.uk/medicines/paracetamol/>

### *Available as*



- Tablets and caplets (500mg), capsules (500mg), soluble tablets (120mg, 500mg), oral suspension (120mg/5ml, 250mg/5ml), Fastabs 250mg, suppositories (60mg, 125mg, 250mg, 500mg and other strengths available from 'specials' manufacturers or specialist importing companies) and intravenous infusion (10mg/ml in 50ml and 100ml vials).

## Parecoxib

### Use:

- Injectable NSAID
- Acute pain when the enteral route is unavailable
- Co-analgesic in cancer-related bone pain when the enteral route is unavailable

### Dose and route:

By intravenous, deep intramuscular or subcutaneous bolus

- **Child 10-40kg:** 500microgram/kg/dose-1mg/kg/dose every 12 hours (maximum 40mg/dose)
- **40kg and over:** 20-40mg/dose every 12 hours

By continuous subcutaneous infusion

- **Child 10-40kg:** 1-2mg/kg/24hours (maximum 80mg/24hours)
- **40kg and over:** 40-80mg/24hours

### Notes:

Pro-drug of the selective COX-2 inhibitor valdecoxib

#### *Licensing*

- Licensed in adults for short term management of post-operative pain. Not licensed in children

#### *Therapeutics*

- Celecoxib may be used as an enteral alternative

#### *Contraindications, cautions*

- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure
- Contraindicated in hypersensitivity to parecoxib or other NSAIDs

#### *Side effects*

- All NSAIDs are associated with serious gastro-intestinal toxicity. Parecoxib is associated with low risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The

greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.

*Hepatic and renal impairment*

- Reduce dose by 50% or avoid in severe renal impairment, reduce dose by 50% in moderate liver impairment, avoid in severe liver impairment

*Pharmacokinetics*

- Onset of action 10–15min (IV/IM), duration of action 6–12hours

*Interactions*

- Moderate inhibitor of cytochrome P450 enzymes CYP2C19 and CYP2D6. May increase levels drugs metabolised by these enzymes including amitriptyline, fluoxetine, haloperidol, hydromorphone, levomepromazine, omeprazole, oxycodone, risperidone, tapentadol and tramadol.
- Metabolised by CYP3A4 and CYP2C9. Levels may be increased by drugs that inhibit these enzymes including erythromycin and sodium valproate. Levels may be reduced by drugs which induce this enzyme including carbamazepine, phenobarbital and phenytoin.

*Administration*

- Intravenous, subcutaneous or intramuscular injection: reconstitute 40mg vial with 2ml 0.9% Sodium chloride or 5% dextrose to give solution for injection of concentration 20mg/ml. IV bolus injection is given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle
- For continuous subcutaneous infusion dilute with sodium chloride 0.9% to maximal volume in a 30ml syringe. Do not mix with other drugs in a syringe driver

*Available as*

- 40mg vial powder for solution for injection

## 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:** 0.8ml/kg as a single dose.
- **1 month and over:** 0.8ml/kg, maximum 20ml as a single dose.

### Notes:

#### *Licensing*

- Paraldehyde enema for rectal use is an unlicensed formulation and route of administration.

#### *Contraindications, cautions*

- Contra-indicated in gastric disorders and in colitis.

#### *Side effects*

- Rectal administration may cause skin irritation.

#### *Pharmacokinetics*

- Mean half-life 7.5 hours

#### *Patient information*

- See Medicines for Children leaflet "Paraldehyde (rectal) for stopping seizures"  
<https://www.medicinesforchildren.org.uk/medicines/rectal-paraldehyde-for-stopping-seizures/>

#### *Available as*

- Paraldehyde enema: premixed solution of paraldehyde in olive oil in equal volumes from 'special-order' manufacturers or specialist importing companies.

## Phenobarbital

### Use:

- Epilepsy including status epilepticus
- Neonatal convulsive status epilepticus: step 3 (after 2<sup>nd</sup> benzodiazepine) in APLS protocol
- Commonly used first line for seizures in neonates
- Palliation of intractable seizures in end-of-life care
- Adjuvant in cerebral irritability
- Sedation
- Agitation refractory to midazolam in end-of-life care

### Dose and route:

#### Status epilepticus, seizures or agitation in end-of-life care

By mouth, intramuscular bolus, slow intravenous injection or subcutaneous infusion

#### Loading dose

- Used to reach steady state quickly and avoid late toxicity due to accumulation. Phenobarbital doses will take between 5 and 30 days to achieve steady state unless a loading dose is given.
- **All ages:** 20mg/kg/dose, maximum 1g, by mouth, intramuscular bolus, slow intravenous injection or subcutaneous infusion over at least 20 minutes (but see notes below)
- In view of concerns regarding respiratory depression in patients actively dying some centres administer an initial half-loading dose of 10mg/kg followed by a further loading dose, if required, after 1-2 hours.

#### On-going treatment

- **Neonate:** 2.5-5mg/kg once or twice daily as maintenance.
- **Child 1 month-11 years:** 2.5-5mg/kg, maximum 300mg/dose, once or twice daily. Total daily dose can also be given as a continuous infusion/24hours.
- **Child 12 years and over:** 300mg twice daily. Total daily dose can also be given as a continuous infusion/24hours.

#### Epilepsy, cerebral irritability

By mouth:

- **Neonate:** 2.5-5mg/kg once or twice daily
- **Child 1 month-11 years:** 1–1.5mg/kg twice daily, increased gradually as required, usual maintenance dose 2.5-4mg/kg once or twice daily

- **12 years and over:** 60–180mg once daily

**Notes:**

*Licensing*

- Licensed for seizures. Not licensed for agitation in end-of-life care.

*Therapeutics*

- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- 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.

*Monitoring*

- Monitoring therapeutic levels may not be appropriate depending on the indication for administration and because tolerance occurs.

*Side effects*

- Sedation, paradoxical agitation, confusion, respiratory depression, movement disorders
- Associated with osteopenia and increased risk of fractures.

*Pharmacokinetics*

- Elimination half-life of 2-6 days in adults, 1-3 days in children.

*Interactions*

- Induces cytochrome P450 enzyme CYP3A4. Reduces levels of numerous drugs including alfentanil, buprenorphine, carbamazepine, dexamethasone, fentanyl, ketamine, midazolam and paracetamol. *This list is not exhaustive –seek advice.*

*Administration*

- 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. Dilute injection solution 1 in 10 with water for injections (i.e. to maximum concentration of 20mg/ml) before intravenous or subcutaneous administration. Administer intravenously at not more than 1mg/kg/minute.

*Patient information*

- See Medicines for Children leaflet “Phenobarbital for preventing seizures”.  
<https://www.medicinesforchildren.org.uk/medicines/phenobarbital-for-preventing-seizures/>

*Available as*

- Tablets (15mg, 30mg, 60mg), oral elixir (15mg/5ml) and injection (15mg/ml, 30mg/ml, 60mg/ml and 200mg/ml). The licensed oral elixir of 15mg/5 ml contains alcohol 38% and it is preferable to obtain an alcohol free oral liquid (usually 50mg/5ml) via one of the specials manufacturers.

*CD*

- Schedule 3 CD (CD No Register Phenobarbital).

## Phenytoin

### Use:

- Epilepsy: status epilepticus, tonic-clonic seizures, focal seizures and neonatal seizures
- Neuropathic pain

### Dose and route:

#### Epilepsy, neuropathic pain

By mouth or short intravenous infusion

- **Neonate:** Initial intravenous loading dose 18mg/kg then 2.5-5mg/kg twice daily by mouth adjusted according to response and plasma phenytoin levels. Usual maximum 7.5mg/kg twice daily.
- **1 month-11 years:** 1.5-2.5mg/kg twice daily adjusted according to response and plasma phenytoin levels. Usual target maintenance dose to 2.5-5mg/kg twice daily. Usual maximum dose of 7.5mg/kg twice daily or 300mg daily.
- **12 years and over:** 75-150mg twice daily adjusted according to response and plasma phenytoin levels. Usual target maintenance dose 150-200mg twice daily. Usual maximum dose of 300mg twice daily.

#### Status epilepticus

By short intravenous infusion

- **Neonate:** Loading dose 20mg/kg, then 2.5-5mg/kg/dose twice daily adjusted according to response and plasma phenytoin levels.
- **1 month-11 years:** Loading dose 20mg/kg, then 2.5-5mg/kg twice daily adjusted according to response and plasma phenytoin levels.
- **12 years and over:** Loading dose 20mg/kg, maximum 1g, then 150mg twice daily adjusted according to response and plasma, phenytoin levels

### Notes:

- Membrane stabiliser.

#### Licensing

- Suspension 90mg in 5ml is a 'special' and unlicensed. Other preparations are licensed for use in children as an anticonvulsant.

#### Therapeutics

- Third or fourth line for epilepsy and for neuropathic pain

- Oral doses are usually as effective as intravenous above 2 weeks old. Older babies may need higher doses.
- Cross-sensitivity is reported with carbamazepine.
- Avoid abrupt withdrawal.
- Consider vitamin D supplementation in patients at risk of osteopenia or vitamin D deficiency.
- Prescribe oral preparations by brand name: bioavailability may vary with brand.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

#### *Side effects*

- Associated with osteopenia and increased risk of fractures. Consider vitamin D supplementation with long term use.
- Arrhythmias, hypotension and respiratory depression with parenteral use

#### *Pharmacokinetics*

- Narrow therapeutic index, unpredictable half-life, and non-linear relationship between dose and plasma-drug concentration. Marked variation in rate of elimination, especially in the first few weeks and months of life.
- Oral bioavailability 90-95% is roughly equivalent to intravenous, plasma half-life 7-42 hours. Poor rectal absorption.

#### *Interactions*

- Induces cytochrome P450 enzymes CYP1A2 and CYP3A4. Reduces levels of numerous drugs including alfentanil, buprenorphine, carbamazepine (also increasing levels of phenytoin), dexamethasone, diazepam, fentanyl, ketamine, melatonin, midazolam and paracetamol. *This list is not exhaustive –seek advice.*
- Long term use is associated with significant side effects. No more effective than other anti-epileptics but doses can be titrated quickly.

#### *Hepatic impairment, renal impairment*

- Reduce dose in hepatic impairment. Monitor carefully if reduced albumin or protein binding e.g. in renal failure.

#### *Administration*

- Administer infusions over at least 20 minutes and at a rate not exceeding 1mg/kg/minute, maximum 50mg/minute. Monitor ECG and blood pressure during administration.
- Dilute to a concentration not exceeding 10mg/ml with Sodium Chloride 0.9% for intravenous infusion. Administer into a large vein through an in-line filter (0.22–0.50 microns); complete administration within 1 hour of preparation. Flush intravenous line with Sodium Chloride 0.9% before and after administration,
- Preparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base (such as Epanutin Infatabs® and Epanutin® suspension); 100mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92mg 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.

*Patient information*

- See Medicines for Children leaflet “Phenytoin for preventing seizures”.  
<https://www.medicinesforchildren.org.uk/medicines/phenytoin-for-preventing-seizures/>

*Available as*

- Tablets (phenytoin sodium 100mg, generic), capsules (phenytoin sodium 25mg, 50mg, 100mg, 300mg), Epanutin® Infatabs (chewable tablets of phenytoin base 50mg), oral suspension (Epanutin® phenytoin base 30mg/5ml, and 90mg/5ml phenytoin base available as an ‘unlicensed special’), and injection (phenytoin sodium 50mg/ml generic)

## Phosphate (rectal enema)

### Use:

- Constipation refractive to other treatments.

### Dose and route:

By rectum:

Phosphate enema BP Formula B (with standard or long rectal tube):

- **Child 3-6 years:** 45-65ml once daily.
- **Child 7-11 years:** 65-100ml once daily.
- **12 years and over:** 100-128ml once daily.

Cleen® (previously Fleet®) Ready to Use enema:

- **Child 3-6 years:** 40-60ml once daily.
- **Child 7-11 years:** 60-90ml once daily.
- **12 years and over:** 90-118ml once daily.

### Notes:

#### *Therapeutics*

- Onset of action 2-5 minutes

#### *Contraindications, cautions*

- Contraindicated in acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption).
- Use only in faecal impaction if all oral medications, and rectal sodium citrate have failed.

#### *Side effects*

- Risk of dehydration and electrolyte disturbance.
- Case reports of hyperphosphataemia and tetany following use of phosphate enemas in children. Risk is likely to be increased with use more than once or twice per week or higher doses.

#### *Administration*

- May be warmed to body temperature in a water bath prior to administration

#### *Available as*

- Phosphate enema BP Formula B (with standard or long rectal tube), Cleen® Ready to Use enema

## Pregabalin

### Use:

- Epilepsy (focal seizures with or without secondary generalisation)
- Peripheral and central neuropathic pain
- Generalised anxiety disorder
- Restless legs syndrome in chronic kidney disease
- Pruritus associated with burns

#### Important safety information

#### **MHRA/CHM advice: Pregabalin (Lyrica®): reports of severe respiratory depression (February 2021)**

Pregabalin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, and concomitant use of central nervous system (CNS) depressants might be at higher risk of experiencing severe respiratory depression and dose adjustments may be necessary in these patients.

### Dose and route:

#### **Neuropathic pain and pruritus, adjunctive therapy for focal seizures, anxiety, restless legs**

By mouth:

- **Child 1 month- 15 years:** 1mg/kg/dose twice daily

Increase every 3-7 days by 500micrograms/kg/dose until desired therapeutic effect or side effects experienced.

Initial maximum 5mg/kg twice daily

Younger children under 30kg and especially those under 6 years may require up to 15mg/kg/day. Maximum 300mg twice daily

- **Adult 16 years and over:** 75mg twice daily

Increase every 3-7 days by 75mg/dose until desired therapeutic effect or side effects experienced.

Maximum 300mg twice daily

**Gabapentin to Pregabalin switch for neuropathic pain**

See Appendix 5

**Notes:***Licensing*

- Licensed in adults as an adjunct for partial seizures; for the treatment of peripheral and central neuropathic pain and for the treatment of generalised anxiety disorder. Not licensed for use in children or adolescents less than 18 years of age.

*Therapeutics*

- Binds to the alpha-2 subunit of voltage gated calcium channels in the CNS thus inhibiting the release of excitatory neurotransmitters. Six times greater receptor affinity than gabapentin
- Younger children less than 6 years may need up to 15mg/kg/day particularly for seizures
- Do not stop abruptly: discontinue gradually over a minimum of one week

*Hepatic impairment, renal impairment*

- Excreted unchanged via kidneys, reduce dose in renal impairment. Recommended maximum doses in renal impairment:

Body-weight	Mild renal impairment Creatinine clearance 31-60ml/min	Moderate renal impairment Creatinine clearance 15-30ml/min	Severe renal impairment Creatinine clearance <15ml/min
Less than 30kg	7mg/kg/24hours	3.5mg/kg/24hours	1.4mg/kg/24hours
More than 30kg	5mg/kg/24hours	2.5mg/kg/24hours	1mg/kg/24hours

- No dose modification required in hepatic impairment

*Pharmacokinetics*

- Oral bioavailability 90% or greater. Peak plasma concentrations occur within 1.5 hours.
- Drug clearance is faster in children under 30 kg. Higher doses and/or more frequent dosing interval may therefore be needed in younger children, particularly those under 6 years of age

*Side effects*

- 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.
- Pregabalin may exacerbate seizures in patients with absence or myoclonic seizures (including juvenile myoclonic epilepsy), tonic or atonic seizures, Dravet syndrome, Lennox-Gastaut syndrome, and myoclonic-atonic seizures.

*Administration*

- Use the oral solution for administration via an enteral tube. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

*Available as*

- Oral capsules (25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg and oral solution (20mg/ml).
- Schedule 3 controlled drug although exempt from safe storage requirements.

## Promethazine hydrochloride

### Use:

- Sleep disturbance.
- Mild sedation
- Symptomatic relief of allergy
- Nausea and vomiting (including motion and opioid-induced), and vertigo
- Sedation in neonatal intensive care

### Dose and route:

Important safety information

**MHRA/CHM advice: Over-the-counter cough and cold medicines for children (April 2009)**

Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

**Contraindications**

Promethazine should not be given to children under 2 years, except on specialist advice, due to the potential for fatal respiratory depression

### Symptomatic relief of allergy:

By mouth:

- **6- 23 months:** 2.5mg–5mg twice daily (on specialist advice)
- **Child 2- 4 years:** 5mg twice daily or 5-15mg at night.
- **Child 5- 9 years:** 5–10mg twice daily or 10–25mg at night.
- **10 years and over:** 10–20mg 2–3 times daily or 25mg at night increased to 25mg twice daily if necessary.

### Sedation (short term use):

By mouth:

- **6- 23 months:** 5-10mg at night (on specialist advice)
- **Child 2- 4 years:** 15-20mg at night.
- **Child 5- 9 years:** 20-25mg at night.
- **10 years and over:** 25-50mg at night.

### **Nausea and vomiting (particularly in anticipation of motion sickness)**

By mouth

- **Child 2-4 years:** 5mg twice daily.
- **Child 5-9 years:** 10mg twice daily.
- **Child 10-17 years:** 20-25mg twice daily.

### **Sedation in intensive care**

By mouth, by slow intravenous injection or by deep intramuscular injection

- **Neonate greater than 37 weeks corrected gestational age:** 500microgram/kg –1mg/kg 4 times daily, adjusted according to response
- **Child 1 month-11 years:** 500microgram/kg-1mg/kg 4 times daily, maximum 25mg/dose, adjusted according to response
- **12 years and over:** 25-50mg/dose 4 times daily adjusted according to response

### **Notes:**

- Antihistamine (anti H1) with moderate muscarinic and D2 receptor antagonism. Significant antimuscarinic activity, particularly in neonates

### *Licensing*

- Not licensed for sedation in children under 2 years

### *Therapeutics*

- Has also been used orally for dyspnoea in adults.
- Used in neonatal units on bigger babies for oral sedation when usual IV sedation options ineffective.
- Start at 25% oral doses if administered intravenously or subcutaneously outside intensive care environment.

### *Contraindications, cautions*

- Caution in epilepsy, asthma. Risk of hypotension if co-prescribed with opioid.

### *Side effects*

- Respiratory depression, arrhythmias, movement disorders including neuroleptic malignant syndrome, urinary retention, insomnia, seizures, nausea and vomiting.

### *Pharmacokinetics*

- Oral bioavailability approximately 25%.

### *Hepatic impairment, renal impairment*

- Caution in renal and severe hepatic impairment

*Interactions*

- Risk of drug interactions with other antimuscarinic or sedative drugs.

*Administration*

- 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/24hours. 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.
- Use oral preparation for administration via gastrostomy. Dilute oral preparation with an equal volume of water for jejunal administration. Tablets will disintegrate if shaken in water for 5 minutes.

*Available as*

- Promethazine hydrochloride tablets (10mg, 25mg), oral elixir (5mg/5 ml), and injection (25mg/ml). (Promethazine teoclate tablets also available, 25mg, licensed for nausea, vertigo and labyrinthine disorders. Slightly longer acting than promethazine hydrochloride and dosing slightly different).

## Propantheline bromide (NEW)

### Use:

- Smooth muscle spasm (bladder and gastrointestinal tract)
- Anti-secretory
- Hyperhidrosis

### Dose and route:

By mouth

Take at least one hour before food

- **1 month-11 years:** 300micrograms/kg/dose, maximum 15mg, 3-4 times daily
- **12 years and over::** 15mg three times daily *and* 30mg at night, maximum 120mg/day

### Notes:

- Quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine

### *Licensing:*

- Not licensed for use in children

### *Therapeutics*

- Acts by two distinct mechanisms: non-specific acetylcholine antagonist at muscarinic M1–3 receptors, *and* a direct musculotropic effect causing relaxation of smooth muscle.
- Possible clinical benefits include decreased respiratory tract secretions, decreased gastric acid production, smooth muscle relaxation. Specific benefits for hyperhidrosis (excessive sweating) and gustatory sweating are attributed to its antagonism of acetylcholine at M3 receptors of glandular tissue.

### *Contraindications, cautions*

- Contraindicated in gastro-intestinal obstruction and ileus, urinary retention, myasthenia gravis
- Caution in arrhythmias, cardiac failure, pyrexia, ulcerative colitis, gastro-oesophageal reflux

### *Side effects*

- Antimuscarinic side effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.

### *Administration*

- Can be administered via gastrostomy. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

### *Available as*

- Tablets 15mg, oral suspension and oral solution from special-order manufacturers.



## Prucalopride (NEW)

### Use:

- Prokinetic agent for treatment of constipation when laxatives are ineffective / inadequate
- Second line prokinetic for upper gastrointestinal dysmotility

### Dose and route:

By mouth

- **Child up to 12 years or less than 50kg:** 30-40micrograms/kg/dose, maximum single dose 2mg, once daily
- **12 years and over and 50kg or over:** 2mg once daily

### Notes:

- Selective 5-HT<sub>4</sub> receptor agonist with an enterokinetic effect increasing GI motility.

### *Licensing:*

- Not licensed for use in children under 18 years of age.

### *Contraindications, cautions*

- Contraindicated in Crohn's disease; intestinal obstruction; intestinal perforation; toxic megacolon; ulcerative colitis.
- Caution in history of arrhythmias

### *Hepatic impairment, renal impairment*

- Reduce dose in severe renal and/or hepatic impairment.

### *Side effects:*

- Headache, dizziness, fatigue and gastrointestinal symptoms (abdominal pain, decreased appetite, GI discomfort, nausea and diarrhoea). Adverse effects occur predominantly at the start of therapy and usually disappear within a few days within continued treatment.

### *Administration:*

Tablets may be crushed and dispersed in water to aid administration (off-label) but may have an unpleasant taste. No information on administration via an enteral feeding tube.

### *Available as*

- 1mg and 2mg tablets.

## Risperidone

### Use:

- Severe neuro-irritability
- Dystonia and dystonic spasms refractory to first and second line treatment
- Delirium
- Short term treatment of persistent aggression in conduct disorder in children and in autism or moderate to severe dementia
- Psychosis in Batten's disease
- Treatment of acute mania or psychosis (under specialist supervision)

### Dose and routes

#### Severe neuro-irritability, refractory dystonia, delirium, aggression

By mouth:

- **Child 1 month-11 years, body-weight up to 50kg:** 10micrograms/kg once daily, maximum 500micrograms/dose, increasing if necessary to 20micrograms/kg once daily after 3-7 days

Increase gradually if required, every 7-14 days in increments of 10micrograms/kg/day to a maximum of 60micrograms/kg/day, maximum 3mg/day

- **12 years and over, body-weight over 50kg:** 500micrograms once daily increasing if necessary to 1mg once daily after 3-7 days

Increase gradually if required, in increments of 500micrograms every 7-14 days to a maximum of 3mg/day

#### Acute mania or psychosis (under specialist supervision), psychosis in Batten's disease

Higher doses, more rapid titration

By mouth:

- **Child 1 month-11 years, body-weight up to 50kg:** 10micrograms/kg, maximum 500micrograms/dose, twice daily; increased on day 2 to 20micrograms/kg, maximum 1mg/dose, twice daily and 30micrograms/kg, maximum 1.5mg/dose, twice daily from day 3

Increase further if required, and as tolerated. Usual maximum 3mg twice daily

- **12 years and over, body-weight over 50kg:** 500micrograms twice daily, increased on day 2 to 1mg, twice daily and 1.5mg twice daily from day 3

Increase further if required, and as tolerated. Usual maximum 3mg twice daily

### Notes

- Dopamine D2, 5-HTA, alpha-1 adrenoceptor and histamine-1 receptor antagonist.

### *Licensing*

- Not licensed for use in children for psychosis, mania, or autism..

### *Therapeutics*

- Usual maintenance dose in adolescents and adults with psychosis or mania is 4-8mg/day.
- Children with Juvenile Battens Disease may need up to 1.5mg 3 times daily during crises with hallucinations: this dose can be reduced or stopped as symptoms settle (episodes usually last 1-6 weeks).
- Maximum adult dose 16mg/day however doses above 10mg/day have not been shown to be more effective and side effects are more likely.
- Some experience as an anti-emetic in refractory nausea and vomiting in adults; not evaluated in children
- Total daily dose can be given once at bedtime.

### *Contraindications, cautions*

- 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.

### *Side effects*

- Weight gain. Other common side effects include anxiety, depression, sleep disorders, hypertension, oedema, malaise, constipation.
- Neuroleptic malignant syndrome

### *Hepatic impairment, renal impairment*

- Initial and subsequent doses should be halved in renal or hepatic impairment.

### *Pharmacokinetics*

- Oral bioavailability 99%. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half-life 24 hours. Duration of action 12-48 hours.

### *Administration*

- Oral liquid may be diluted in any non-alcoholic drink except tea. Orodispersible tablets should be placed on the tongue, allowed to dissolve and swallowed. Use oral liquid for administration via enteral feeding tubes. Tablets also disintegrate in water within 5 minutes for easy administration via enteral feeding tubes. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

### *Patient information*

- See Medicines for Children leaflet "Risperidone for psychological disorders".  
<https://www.medicinesforchildren.org.uk/medicines/risperidone-for-psychological-disorders/>

### *Available as*

- Tablets (500micrograms, 1mg, 2mg, 3mg, 4mg, 6mg), orodispersible tablets (500micrograms, 1mg, 2mg, 3mg, 4mg), oral solution 1mg/ml.

## Salbutamol

### Use:

- Breathlessness or wheeze caused by bronchospasm including exacerbations associated with respiratory tract infection.
- Prevention and treatment of chronic lung disease in premature infants
- Hyperkalaemia.

### Dose and route:

#### Exacerbation of reversible airway obstruction, prevention of allergen-or exercise-induced bronchospasm

By aerosol inhalation:

Use via large volume spacer (and a close-fitting face mask in children under 3 years).

- **Child 1 month and over:** 100-200micrograms (1-2 puffs) up to four times daily.

By inhalation of nebulised solution:

- **Neonate:** 1-2.5mg up to four times daily
- **Child 1 month-4 years:** 2.5mg up to four times daily
- **5-11 years:** 2.5-5mg, up to four times daily.
- **12 years and over:** 5mg, up to four times daily

#### Emergency treatment of moderate to severe acute asthma

N.B. Use in this context typically given in hospital setting to enable escalation of treatment if required. See separate detailed guidance in standard texts for use in acute life-threatening asthma

By aerosol inhalation:

- **Child 1 month and over:** 200-1000micrograms (2–10 puffs), each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer (and a close-fitting face mask in children under 3 years).

By inhalation of nebulised solution (*inpatient settings only*)

- **Child 1 month-4 years:** 2.5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.

- **5-11 years:** 2.5-5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.
- **12 years and over:** 5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.

## Hyperkalaemia

See separate detailed guidance in standard texts

## Notes

Short acting beta 2 adrenergic receptor agonist

### *Licensing*

- Salbutamol is not licensed for use in hyperkalaemia; injection is not licensed for use in children.

### *Therapeutics*

- Spirometry should normally be used to confirm a possible underlying asthma diagnosis.
- 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.
- 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. No evidence of efficacy in infection-related bronchospasm in infants
- Oral liquid is generally used only in the context of slowing rate of degradation of motor neurone proteins in neuromuscular disease. Seek specialist advice
- In children over the age of 5 years with mild and moderate acute asthma attacks, a pressurised metered-dose inhaler with a spacer is at least as effective as nebulisation.
- Ipratropium bromide is an appropriate alternative if side effects prevent use
- 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.

### *Contraindications, cautions*

- Risk of tachycardia and risk of QT prolongation at increasing doses.

### *Side effects*

- Increased heart rate; feeling “edgy” or agitated; tremor. Rarely paradoxical bronchospasm can occur in response to beta-2-adrenoceptor agonists, hypokalaemia

### *Pharmacokinetics*

- Onset of action 5 minutes via inhalation of aerosol, 3-5 minutes nebulised. Peak response 0.5-2 hours. Duration of action 4-6 hours. Only 10-20% of inhaled dose reaches lower airways.

### *Interactions*

- Increased risk of hypokalaemia with corticosteroids, diuretics, theophylline.

*Administration*

- Inhaled product should be used with a suitable spacer device. The carer, and child where appropriate, 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 nebulisers 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% Sodium chloride. Salbutamol can be mixed with nebulised solution of ipratropium bromide.

*Patient information*

- See Medicines for Children leaflet "Salbutamol for asthma and wheeze".  
<https://www.medicinesforchildren.org.uk/medicines/salbutamol-inhaler-for-asthma-and-wheeze/>

*Available as*

- Nebuliser solution (2.5mg/2.5ml, 5mg in 2.5 ml), respirator solution (5mg/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 micrograms per puff., injection (500 micrograms/ml), intravenous infusion (1mg/ml) oral solution (2mg/5ml ), tablets (2mg and 4mg).

## Senna

### Use:

- Constipation (stimulant laxative)

### Dose and route:

By mouth:

Start at low dose, increasing as necessary after 24–48 hours

- **Child 1 month-3 years:** 3.75-15mg once daily, adjusted according to response.
- **4-5 years:** 3.75-30mg once daily, adjusted according to response.
- **6-17 years:** 7.5-30mg once daily, adjusted according to response.

### Notes:

- Stimulant laxative acting on large bowel.

#### *Licensing*

- Oral solution is not licensed for use in children < 2 years and tablets are not licensed for use in children <6 years

#### *Therapeutics*

- Improves intestinal motility and increases water secretion into bowel lumen. Senna passes unchanged into large bowel. Hydrolysed by bacterial flora in the large bowel to yield the active compound.
- NICE Guidance CG99: Constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives prior to a trial of a stimulant laxative. However, senna is considered the drug of first choice for opioid induced constipation in palliative care
- Optimise dose before adding a second agent
- Doses can be exceeded on specialist advice: opioid induced constipation often requires higher doses than in manufacturer's Product Information.
- Onset of action 8-12 hours.
- Available in the UK as an "over the counter" medicine for short courses in adults only

#### *Contraindications, cautions*

- Contraindicated in atony, intestinal obstruction, undiagnosed abdominal pain

#### *Side effects*

- Abdominal pain. Prolonged use or excessive use can cause hypokalaemia.

#### *Administration*

- Oral liquid may be administered via an enteral feeding tube; flush well before and after the dose. Therapeutic effect will be unaffected by jejunal administration.

*Patient information*

- See Medicines for Children leaflet “Senna for constipation”.  
<https://www.medicinesforchildren.org.uk/medicines/senna-for-constipation/>

*Available as*

- Tablets (7.5mg sennoside B) and oral suspension (7.5mg/5ml sennoside B)



## Sodium Citrate

### Use:

- Constipation (osmotic laxative)

### Dose and routes:

By rectum

#### *Micolette Micro-enema*

Sodium citrate 450mg, sodium lauryl sulfoacetate 45mg, glycerol 625mg, together with citric acid, potassium sorbate, and sorbitol in a viscous solution, in 5ml

- **Child 3 years and over:** 5–10ml as a single dose

#### *Micralax Micro-enema*

Sodium citrate 450mg, sodium alkylsulfoacetate 45mg, sorbic acid 5mg, together with glycerol and sorbitol in a viscous solution in 5ml

- **Child 3 years and over:** 5ml as a single dose

#### *Relaxit Micro-enema*

Sodium citrate 450mg, sodium lauryl sulfate 75mg, sorbic acid 5mg, together with glycerol and sorbitol in a viscous solution in a 5ml single dose pack with nozzle.

- **Child 1 month and over:** 5ml as a single dose (insert only half nozzle length in child 2 years or under).

### Notes

- Osmotic laxative

#### *Licensing*

- Licensed for treatment of constipation for all ages

#### *Therapeutics*

- Usually combined with faecal softener (e.g. sodium lauryl sulphate, sodium alkylsulfoacetate) in micro-enemas.
- Sodium citrate is an osmotic agent. Sodium lauryl sulfoacetate is a faecal softener.
- Used where oral laxatives are ineffective or not feasible. Micro-enema, often used in combination with oral laxatives, particularly in neuromuscular disorders, faecal loading and faecal impaction.

- NICE Guidance for the management of constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives and stimulant laxatives before the use of rectal measures. Sodium Citrate is considered the first line rectal measure, in preference to phosphate enemas.
- Usually acts within 15 minutes of administration

*Contraindications, cautions*

- Contraindicated in acute gastro-intestinal conditions
- Caution: can cause harmful sodium and water retention in susceptible patients.

*Side effects*

- Abdominal discomfort

*Available as*

- Micro-enema (5ml). All currently marketed preparations include sodium citrate 90mg/ml, but other constituents vary.

## Sodium Picosulfate

### Use:

- Constipation (stimulant laxative).

### Dose and routes:

By mouth:

- **Child 1 month-3 years**

Less than 10kg: 250micrograms/kg once daily

More than 10kg: 2.5mg once daily

Increase as necessary according to response to a suggested maximum of 10mg daily

- **Child 4 years and over:** Initial dose of 2.5mg once daily increase as necessary according to response to a suggested maximum of 20mg daily.

### Notes

- Stimulant laxative

#### *Licensing*

- Oral suspension is licensed for use in children; capsules are not licensed for use in children less than 4 years of age.

#### *Therapeutics*

- NICE Guidance CG99: Constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives prior to a trial of a stimulant laxative. However, for opioid induced constipation in palliative care, senna is a considered the first line choice. If ineffective at first, dose should be optimised and only add a second agent if not adequately effective.
- Effectiveness dependent upon breakdown by gut flora-previous effectiveness may therefore be lost during courses of antibiotics and ensuing altered gut flora.
- Onset of action 6-12 hours.

#### *Contraindications, cautions*

- Contraindicated in intestinal obstruction and undiagnosed abdominal pain

#### *Side effects*

- Prolonged use or excessive use can cause hypokalaemia.

#### *Administration*

- Use the liquid preparation for administration via an enteral feeding tube; 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.

*Patient information*

- See Medicines for Children leaflet “ sodium picosulfate for constipation”  
<https://www.medicinesforchildren.org.uk/medicines/sodium-picosulfate-for-constipation/>

*Available as*

- Oral solution (5mg/5ml) and capsules (as Dulcolax PicoPerles 2.5mg). Also available mixed with Magnesium citrate for bowel evacuation prior to procedures (Picolax and Citrafleet).

## Sucralfate

### Use:

- Prophylaxis of stress ulcer.
- Prophylaxis of bleeding from oesophageal or gastric varices
- Adjunct in the treatment of: oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration,
- Upper gastro intestinal tract bleeding of unknown cause.
- Haemostasis (topical use).

### Dose and route:

#### Prophylaxis and adjunctive treatment of upper GI tract bleeding

By mouth

- **Child 1 month-1 year:** 250mg four to six times daily.
- **2-11 years:** 500mg four to six times daily.
- **12-14 years:** 1g four to six times daily.
- **15 years and over:** 1g six times daily (maximum 8g/day).

#### Topical haemostasis

- Sucralfate suspension (1g/5ml) can be applied to the affected area twice daily e.g. as mouth wash, orally for oesophageal lesions, rectally for rectal lesions.
- Sucralfate paste (2 x 1g tablets crushed in 5ml aqueous jelly lubricant, or water) applied to the affected area twice daily

### Notes:

- Complex of aluminium hydroxide and sulphated sucrose.

#### *Licensing*

- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration.

#### *Therapeutics*

- In the gut it seems to act by protecting mucosa from acid-pepsin attack. Minimal antacid properties. Acts locally and is minimally absorbed.
- Spread doses evenly throughout waking hours.

#### *Side effects*

- Case reports of bezoar formation with sucralfate.

*Contraindications, cautions*

- 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.

*Pharmacokinetics*

- Onset of action 1-2 hours, duration of action 6 hours.

*Administration*

- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by at least 1 hour to avoid formation of an insoluble complex that may block fine-bore feeding tubes. By mouth sucralfate should be given 1 hour before meals to reduce chance of bezoar formation. Suggest diluting with water before administration. Not appropriate for jejunal administration as the site of action is gastric and duodenal.
- Tablets may be crushed and dispersed in 10-15 ml water.

*Available as*

- Oral suspension (1g/5ml special order), tablets (1g). Oral suspension, cream, powder and enema available as special order.

## Sucrose

### Use:

- Analgesia for procedural pain in babies.

### Dose and route:

By mouth:

- **Neonate over 32 weeks:** 0.5-2ml of 24% sucrose orally 2 minutes before the procedure (alternatively a pacifier/dummy could be placed in the sucrose solution).

Incremental doses 0.1ml can be used up to the maximum of 2ml. Multiple doses can be given during a single procedure.

- **Preterm infants:** administer a maximum of 4 times per 24 hours
- **Neonates and babies:** administer a maximum of 8 times in 24 hours

### Notes

#### *Licensing*

- Algopedol® is licensed for use in term and preterm infants less than 4 months of age

#### *Therapeutics*

- Dextrose 25% in similar volumes may achieve the same effect.
- Effect enhanced when combined with other non-pharmacological techniques for providing analgesia including non-nutritive sucking and behavioural measures such as swaddling.
- Limited evidence to guide dosing in very premature babies
- May have a role in managing pain in infants up to 12 months.
- 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.

#### *Contraindications, cautions*

- Contraindicated in babies with oesophageal atresia, tracheo-oesophageal fistula, confirmed or suspected intra-abdominal pathology (e.g. NEC), fructose intolerance.
- Use with caution in infants with altered gag or swallow reflex or swallowing problems, cardio-respiratory instability or any major GI pathology.

#### *Administration*

- 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.

- Infants who are nil by mouth (NBM) or have an endotracheal tube in situ can (with medical approval) have the dose of oral sucrose applied with a small swab directly onto the tongue.
- Not appropriate for administration via feeding tube

*Available as*

- Preservative-free oral solution of sucrose 24% (Algopedol®) in 2 ml vials for single patient use, or sucrose 24% (Sweet-Ease) in 15ml cups which can be used to dip a pacifier into or draw up into dropper/syringe.



## Tapentadol

### Use:

- Opioid analgesic

#### Important safety information

##### For all opioids

##### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

#### Pain in opioid naïve patients

By mouth using immediate release preparations

- **Child 2-17 years and body-weight over 16 kg:** 1.25mg/kg/dose every 4 hours. Maximum initial dose 50mg, can be increased to body-weight adjusted dose for subsequent dosing

The dose for children with a high BMI must not exceed the calculated dose for a body-weight at the 97.5 percentile for the given age.

Maximum total daily dose 7.5mg per kg body-weight (\*see notes below)

- **18 years and older:** Initially 50mg every 4–6 hours, adjusted according to response, on the first day of treatment, an additional dose of 50mg may be taken 1 hour after the initial dose; maximum 700mg in the first 24 hours; maximum 600mg daily.

#### By mouth using modified release preparations

- **18 years and above:** Initially 50mg every 12 hours, adjusted according to response; maximum 500mg daily.

**Notes:**

- Opioid analgesic. Approximately 3 times less potent than morphine i.e. 50mg oral tapentadol is approximately equivalent to 15mg oral morphine

*Licensing*

- Tapentadol oral solution is licensed for the relief of moderate to severe acute pain in children from 2 years of age (>16 kg body-weight) for a maximum of 72 hours. Use of tablet formulations or for treatment of chronic pain or for a duration >72 hours in children is off-label. Data on safety and efficacy of long-term use in children is not yet available and clinical trials are on-going.
- Tapentadol oral solution, immediate-release and modified-release tablets are licensed in adults for treatment of moderate to severe acute and chronic pain.

*Therapeutics*

- Dual action centrally acting opioid analgesic; agonist at the  $\mu$ -opioid receptor and inhibitor of noradrenaline reuptake. The latter enhances the action of the descending pain inhibitory pathway contributing to a synergistic analgesic effect.
- Care needed if switching from another  $\mu$ -agonist to tapentadol as this may cause low-grade opioid withdrawal. As required doses of the original opioid should be used to counter this (e.g. give an immediate release product at 25-50% of the original dose).
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

*Cautions*

- MHRA/CHM advice: Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines (January 2019). Tapentadol can induce seizures and should be prescribed with caution in patients with a history of seizure disorders or epilepsy. Seizure risk may be increased in patients taking other medicines that lower seizure threshold, for example, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics.

*Side effects*

- Potential adverse effects as for other opioids. However GI side effects are reportedly less than with oxycodone or morphine.

*Hepatic and renal impairment*

- Dosage adjustment is not required in mild or moderate renal impairment. not recommended in severe renal impairment (lack of clinical trial data).
- Dosage adjustment is not required in mild hepatic impairment. Reduce initial dose in moderate hepatic impairment. Not recommended in severe hepatic impairment (lack of clinical trial data).

*Pharmacokinetics*

- Based on immediate release tablets-onset of action is less than 1 hour with time to peak serum concentrations around 75 minutes. Duration of action 4-6 hours. Duration of action of modified-release tablets is 12 hours.
- Tapentadol is rapidly and completely absorbed after oral administration. However mean absolute bioavailability after a single-dose administration is ~32% due to extensive first-pass metabolism.
- The major elimination pathway for tapentadol is glucuronide conjugation. Tapentadol does not have any active metabolites.

*Administration*

- Tapentadol oral solution 20mg/ml can be taken undiluted or diluted in water or any non-alcoholic drink. Use the dosing pipette (5ml subdivided in 0.1ml (2mg) intervals) provided to ensure the exact dose can be accurately measured.
- Tapentadol oral solution can be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.
- Tapentadol oral solution contains 2mg/ml propylene glycol.
- Modified-release tapentadol tablets should be swallowed whole; crushing or chewing will lead to a rapid release of an overdose of tapentadol.

*Available as*

- Oral solution 20mg/ml (licensed from 2 years) Palexia®, immediate-release tablets 50mg, 75mg (licensed from 18 years only) Palexia®, Modified-release tablets (licensed from 18 years only) 25mg, 50mg, 100mg, 150mg, 200mg, 250mg Palexia®, Ationdo®. Modified-release capsules (licensed from 18 years only) 50mg, 100mg, 150mg, 200mg, 250mg Tapimio® As for all modified release opioids, brand prescribing is recommended to reduce the risk of confusion and error in dispensing and administration

*CD*

- CD Schedule 2

## Temazepam

### Use:

- Sleep disturbance (short term use), especially where anxiety is a cause.
- Premedication before surgery and investigations

Important safety information

#### For all benzodiazepines

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The **APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and route:

By mouth:

- **Child 12-17 years:** 10-20mg 1 hour before procedures.
- **Adult:** 10-20mg at night. Dose may be increased to 40mg at night in exceptional circumstances.

### Notes:

- GABA mimetic, anxiolytic sedative.

#### *Licensing*

- Tablets not licensed for use in children.

#### *Therapeutics*

- Correct contributory factors to insomnia if possible. Use in association with non-pharmacological methods.

#### *Side effects*

- Can cause paradoxical increased hostility and aggression requiring dose adjustment. Can also paradoxically increase anxiety. May impair judgement and reaction time.

*Contraindications, cautions*

- Contraindicated in severe hepatic impairment (unless in imminently dying)
- Caution in renal impairment, shorter half-life benzodiazepines may be preferable
- Contraindicated in respiratory depression, compromised airway and untreated sleep apnoea syndrome, except in the imminently dying.

*Pharmacokinetics*

- Oral bioavailability at least 90%; peak plasma concentration within 50 minutes of oral administration. Long plasma half-life of 8-15 hours.

*Administration*

- Oral solution may be administered via an enteral feeding tube. If administered via the jejunum monitor for loss of efficacy or increased side effects.

*Available as*

- Tablets (10mg, 20mg) and oral solution (10mg/5 ml).

*CD*

- Schedule 3 controlled drug (CD No register).

## Tizanidine

### Use:

- Skeletal muscle relaxant.
- Chronic severe muscle spasm or spasticity.

### Dose and route:

By mouth

- **Child 18 months-6 years:** 1mg/day in divided doses; increase if necessary, according to response.
- **7-11 years:** 2mg/day in divided doses; increase if necessary, according to response.
- **12 years and over:** 2mg/day in divided doses increasing in increments of 2mg at intervals of 3–4 days

Usual adult total daily dose 24mg. Maximum total daily dose 36mg.

Administer as 3-4 divided doses. Timing and frequency of dosing is specific to individual patient as maximum effect is seen 2-3 hours after administration.

Titrate doses slowly over 2-4 weeks to reduce side effects

### Notes:

#### *Licensing*

- Not licensed for use in children.

#### *Therapeutics*

- Limited research evidence in children. Paediatric doses largely extrapolated from adult doses
- Usually prescribed and titrated by neurologists.
- Peak response not seen until approximately 8 weeks.
- Avoid abrupt withdrawal-risk of rebound hypertension and tachycardia.

#### *Contraindications, cautions*

- Use with caution with drugs known to prolong the QT-interval.

#### *Monitoring*

- Monitor liver function monthly for first 4 months.

#### *Side effects*

- Drowsiness, weakness, hypotension and dry mouth are common side effects.

#### *Hepatic impairment, renal impairment*

- Use with caution in liver disease, monitor liver function regularly.
- Caution in renal impairment

*Interactions*

- Metabolised by cytochrome P450 enzyme CYP1A2. Levels increased by drugs that inhibit this enzyme including ciprofloxacin and possibly famotidine potentially leading to severe hypotension. Levels may be reduced by drugs that induce this enzyme including phenytoin.

*Administration*

- 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. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

*Available as*

- Tablets (2mg, 4mg).

## Tramadol

### Use:

- Weak opioid with additional non-opioid analgesic actions

The WHO now advises there is insufficient evidence to make a recommendation use of weak opioids in children and recommends moving directly from non-opioids to low dose strong opioids for the management of moderate uncontrolled pain in children

Important safety information

#### **For all opioids**

#### **MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)**

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

**The APPM** recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

### Dose and routes

By mouth, subcutaneous, intramuscular or slow intravenous injection:

- **Child 4-11 years:** 1mg/kg/dose every 6 hours. Maximum 50mg/dose.  
Increased if required to 1.5mg/kg/dose every 6 hours and then to 2mg/kg/dose every 6 hours. Maximum 100mg/dose
- **12 years and over:** Initial dose of 50mg every 4-6 hours. Increase if necessary to a maximum of 400mg/day given in divided doses every 4-6 hours.

Total daily dose can also be given as a continuous intravenous or subcutaneous infusion/24hours.

### Notes:

#### *Licensing*

- Not licensed for use in children under 12 years.



### *Therapeutics*

- By mouth tramadol is approximately 1/10 as potent as morphine. However equianalgesic ratios may be unreliable due to inter-individual variation in CYP2D6 activity.
- Has been given by sublingual route at similar doses
- May be helpful in neuropathic pain and visceral hyperalgesia
- Tramadol itself has analgesic properties. It is also metabolized in the liver by CYP2D6 to the active metabolite desmethyltramadol which has a higher affinity for the mu-opioid receptor. Unlike codeine, poor metabolisers experience only slightly diminished analgesic effect. The risk of respiratory depression may be higher in the 5% of the western European population who are ultra-metabolisers. However, the risk is likely to be significantly less than with codeine.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

### *Side effects*

- Causes less constipation and respiratory depression than the equivalent morphine dose. Risk of respiratory depression may be increased in paediatric patients who are obese or have conditions such as obstructive sleep apnoea or severe lung disease, or who are ultrarapid metabolizers of the drug
- Side effects include diarrhoea, retching, fatigue and paraesthesia.

### *Pharmacokinetics*

- Onset of action after an oral dose is 30 to 60 minutes. Duration of action is 4-6 hours.

### *Interactions*

- Analgesic effect may be reduced by ondansetron. Increased risk of serotonin syndrome with co-administration of tramadol and ondansetron

### *Hepatic impairment, renal impairment*

- Avoid or reduce dose

### *Administration*

- Orodispersible tablets should be sucked and then swallowed or they may be dispersed in water. Modified release capsules may be opened and the capsule contents swallowed immediately without chewing.
- Soluble or orodispersible tablets may be dissolved in water for administration via an enteral feeding tube or use the oral drops or disperse capsule contents. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.
- For subcutaneous infusion dilute in sodium chloride 0.9% or water for injection

### *Patient information*

- Patient information see Medicines for Children leaflet "Tramadol for pain"  
<https://www.medicinesforchildren.org.uk/medicines/tramadol-for-pain/>

### *Available as*

- Soluble tablets 50mg, Orodispersible tablets 50mg, Immediate release capsules 50mg, Oral solution 10mg/ml, oral drops 100mg/ml, modified-release 12hr tablets 50mg, 100mg, 150mg, 200mg, 300mg, 400mg, modified release 12hr capsules 50mg, 100mg, 150mg, 200mg, modified-release 24hr tablets 150mg, 200mg, 300mg, 400mg, solution for injection 100mg/2ml
- Brand prescribing of modified release preparations is recommended to reduce the risk of confusion and error in dispensing and administration. Care with prescribing preparations due to availability of both 12-hour and 24 hour modified release formulations

### *CD*

- Schedule 3 CD

## Tranexamic acid

### Use:

- Inhibition of fibrinolysis
- Oozing of blood (e.g. from mucous membranes or capillaries), particularly when due to thrombocytopenia or platelet dysfunction
- Menorrhagia

### Dose and route:

#### Inhibition of fibrinolysis

By mouth:

- **Child 1 month and over:** 15-25mg/kg (maximum dose 1.5 g) 2–3 times daily.

By intravenous injection over at least 10 minutes:

- **Child 1 month and over:** 10mg/kg (maximum dose 1 g) 2-3 times daily.

By continuous intravenous infusion:

- **Child 1 month and over:** 45mg/kg/24hours.

#### Menorrhagia

By mouth:

- **Child 12 years and over:** 1g 3 times daily for up to 4 days.

Up to 4g in divided doses can be used for very heavy bleeding. Treatment should not be initiated until menstruation has started.

#### Prevention or treatment of oral bleeding

For use as mouthwash (5% solution):

- **Child 6 years and over:** 5-10ml 4 times daily for 2 days. Not to be swallowed.

#### Topical treatment of bleeding:

- Apply gauze soaked in 100mg/ml injection solution to affected area.

**Notes:**

*Licensing*

- Injection not licensed for use in children under 1 year or for administration by intravenous infusion.

*Side effects*

- Urinary tract clots resulting from use in presence of haematuria can result in urinary tract obstruction and clot 'colic'
- Diarrhoea, nausea and vomiting

*Hepatic impairment, renal impairment*

- Reduce dose in mild to moderate renal impairment and avoid in severe renal impairment.

*Administration*

- 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 without blockage. No specific information for jejunal administration.
- Parenteral preparation can be used topically.

*Patient information*

- See Medicines for Children leaflet "Tranexamic acid for heavy bleeding during periods" <https://www.medicinesforchildren.org.uk/medicines/tranexamic-acid-for-heavy-bleeding-during-periods/> and Medicines for Children leaflet "Tranexamic acid for the treatment or prevention of bleeding in haemophilia and other clotting problems"
- <https://www.medicinesforchildren.org.uk/medicines/tranexamic-acid-for-the-treatment-or-prevention-of-bleeding-in-haemophilia-and-other-clotting-problems/>

*Available as*

- Tablets (500mg), syrup (500mg/5 ml available from 'specials' manufacturers) and injection (100mg/ml ampoules). Mouthwash only as extemporaneous preparation.

## Trihexyphenidyl

### Uses:

- Dystonia
- Sialorrhoea (drooling)
- Antispasmodic.

### Dose and route:

By mouth

- **Child 3 months and over:** 1–2mg daily in 1-2 divided doses, increased every 3-7 days by 1mg daily; adjusted according to response and side effects, maximum 2mg/kg (or 100mg) daily

Doses needed to control drooling are generally much lower than those needed for dystonia

### Notes:

- Reduces the effects of the relative central cholinergic excess that occurs in dopamine deficiency.

#### *Licensing*

- Not licensed for use in children.

#### *Therapeutics*

- Use in conjunction with careful observation and a full non-drug management programme including positioning, massage, holding, distraction, checking for causes of exacerbations etc. Seek specialist neurological advice.
- May have limited efficacy in children with cerebral palsy and dystonia.
- Start at a low dose and increase gradually to minimise the incidence and severity of side effects.
- 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.

#### *Contraindications, cautions*

- Contraindicated in myasthenia gravis

#### *Side effects*

- Side effects are very common. Mouth dryness, constipation, blurring of vision, dizziness and nausea can occur in 30-50% patients. Less common side effects include urinary retention, tachycardia, confusion, insomnia and with very high doses CNS disturbance including oculogyric crisis

#### *Hepatic impairment, renal impairment*

- Use with caution in children with renal or hepatic impairment.

#### *Pharmacokinetics*

- Onset of action is usually within 1 hour, maximum effect occurs within 2-3 hours and duration of effect approximately 6-12 hours.

*Administration*

- Tablets may be crushed and mixed in soft food.
- Administration with or after food may help minimise gastrointestinal adverse effects
- The oral liquid may be used for administration via feeding tubes. Alternatively the tablets will disperse readily in water. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

*Patient information*

- See Medicines for Children leaflet "Trihexyphenidyl hydrochloride for dystonia"  
<https://www.medicinesforchildren.org.uk/medicines/trihexyphenidyl-hydrochloride-for-dystonia/>

*Available as*

- Tablets 2mg and 5mg; oral liquid 5mg in 5 ml.

## Vitamin K (Phytomenadione)

### Use:

- Treatment of haemorrhage associated with vitamin-K deficiency (seek specialist advice)
- Reversal of coumarin anticoagulant (warfarin) overdose

### Dose and route:

By mouth or intravenous:

- **Neonate:** 100micrograms/kg.
- **Child 1 month and over:** 250-300micrograms/kg (maximum 10mg) as a single dose.

### Notes:

#### *Contraindications, cautions*

- Caution with intravenous use in premature infants less than 2.5 kg, increased risk of kernicterus

#### *Administration*

- Risk of cardiovascular collapse with rapid administration. Preferably dilute with Glucose 5% and give over 15-20 minutes. Can also be given as a slow intravenous injection over 3-5 minutes
- Injection should be protected from the light.

#### *Available as*

- Capsules 1mg, oral drops 200 micrograms/ml and injection 10mg/ml. Many other forms and strengths available from special order manufacturers.

## Appendix 1: Opiate conversion tables

- Opioid conversion tables can be used to calculate approximate equianalgesic doses of opioids when switching from a weak opioid to morphine, or from one strong opioid to another.
- Caution is *always* necessary. Conversion ratios are never more than an approximate guide due to:
  - Wide inter-individual variation in opioid pharmacokinetics
  - Limited data on opioid equi-analgesia in children
  - Differences between opioid pharmacokinetics in adults and children
  - Data largely derived from single dose studies
  - Potential for opioid tolerance related to dose and duration of opioid treatment
  - Direction of switch in opioid
  - Concurrent medications
- If switching from an opioid other than morphine to another opioid, convert the dose of the first opioid to morphine equivalent, and then use that quantity to determine the dose of the second opioid.
- Consider reducing the dose of the new opioid by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation.

### Notes

- Equianalgesic ratios for methadone are dose dependent and highly variable: see methadone monograph
- Mean oral bio-availability of oxycodone is 75% (range 60–87%). For safety, recommended equianalgesic ratios are therefore either rounded down to 1.5:1 or up to 2:1 depending on direction of switch and rounding errors
- Newer systematic review evidence suggests using a ratio of 3:1 when converting morphine from oral to intravenous morphine
- Bioavailability of some drugs may be lower for subcutaneous versus intravenous administration, particularly for infusions. However the APPM recommendation is to assume similar pharmacokinetics for intravenous and subcutaneous dosing.
- Oral tapentadol is approximately 3 times less potent than morphine e.g. 30mg tapentadol is approximately equivalent to 10mg oral morphine. However experience in children is currently too limited to make clear recommendations regarding opioid conversion

## Conversion from oral morphine

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Alfentanil CSCI or CIVI	30:1	Divide 24hour morphine dose by 30	Morphine oral 60mg/24hours ÷ 30 = alfentanil CSCI 2mg/24hours
Morphine oral	Buprenorphine sublingual	80:1	Divide 24hour morphine dose <i>in mg</i> by 80 to give 24hour buprenorphine dose <i>in mg</i>  Then multiply 24hour buprenorphine dose <i>in mg</i> by 1,000 to give 24hour buprenorphine dose <i>in micrograms</i>  <i>Then</i> divide 24hour buprenorphine dose <i>in micrograms</i> into 3 or 4 divided doses for 8 or 6 hourly administration	Morphine oral 60mg/24hours ÷ 80 = buprenorphine SL 0.75mg/24hours  Buprenorphine 0.75mg/24hours x 1000 = buprenorphine 750micrograms/24hours  Buprenorphine 750micrograms/24hours ÷ 3 = 250micrograms 8 hourly  <i>Round down to</i> 200micrograms SL 8 hourly
Morphine oral	Buprenorphine transdermal	100:1	Divide 24hour morphine dose <i>in mg</i> by 100 to give 24hour buprenorphine dose <i>in mg</i>  <i>Then</i> multiply 24hour buprenorphine dose <i>in mg</i> by 1,000 to give 24hour buprenorphine dose <i>in micrograms</i>  <i>Then</i> divide 24hour buprenorphine dose in micrograms by 24 to give patch strength in micrograms/hour	Morphine oral 300mg/24hours ÷ 100 = buprenorphine transdermal 3mg/24hours  Buprenorphine 3mg/24hours x 1000 = buprenorphine 3,000micrograms/24hours  Buprenorphine 3,000micrograms/24hours ÷ 24 = buprenorphine 125micrograms/hour  <i>Round down to</i> 70+35microgram/hour buprenorphine patches
Morphine oral	Diamorphine CSCI or CIVI	6:1	Divide 24hour morphine dose by 6	Morphine oral 30mg/24hours ÷ 6 = diamorphine CSCI 5mg/24hours



## Conversion from oral morphine

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Diamorphine intranasal	3:1	Divide PRN morphine dose by 3	Morphine oral 3mg PRN $\div$ 3 = Diamorphine intranasal 1mg PRN
Morphine oral	Fentanyl CSCI or CIVI	100:1 <sup>29</sup>	Divide 24hour morphine oral <i>in mg</i> dose by 100 to give fentanyl dose in <i>mg/24hours</i>  <i>Then</i> multiply fentanyl dose in <i>mg/24hours</i> by 1000 to convert to <i>micrograms/24hours</i>	Morphine oral 60mg/24hours $\div$ 100 = fentanyl CIVI 0.6mg/24hours CSCI  Fentanyl CIVI 0.6mg/24hours $\times$ 1000 = fentanyl 600micrograms/24hours
Morphine oral	Fentanyl transdermal patch	100:1	Divide 24hour morphine oral dose by <i>in mg</i> 100 to give fentanyl transdermal dose in <i>mg</i>  <i>Then</i> multiply by 1,000 to give fentanyl transdermal dose in <i>micrograms</i>  <i>Then</i> divide by 24 to give fentanyl transdermal dose in <i>micrograms/hour</i>	Morphine oral 90mg/24hours $\div$ 100 = fentanyl transdermal 0.9mg/24hours  Fentanyl 0.9mg/24hours $\times$ 1000 = fentanyl 900micrograms/24hours  Fentanyl 900micrograms/24hours $\div$ 24 = fentanyl 37.5mg/hour = fentanyl 12+25micrograms/hour patches
Morphine oral	Hydromorphone oral	5:1	Divide morphine oral dose by 5	Morphine oral 10mg $\div$ 5 = hydromorphone oral 2mg
Morphine oral	Oxycodone oral	2:1	Divide morphine oral dose by 2	Morphine oral 20mg $\div$ 2 = oxycodone oral 10mg
Morphine oral	Oxycodone CSCI or CIVI	3:1	Divide morphine oral dose by 3	Morphine oral 30mg/24hours $\div$ 3 = oxycodone CSCI or CIVI 10mg/24hours
Morphine oral	Tramadol oral	1:10	<i>Multiply</i> the total daily dose of oral morphine by 10	Morphine oral 10mg $\times$ 10 = tramadol oral 100mg

<sup>29</sup> Some centres use equianalgesic ratio of 150:1 depending on circumstances

**Conversion from continuous intravenous or subcutaneous morphine**

Conversion		Ratio	Calculation	Example
From	To			
Morphine CSCI or CIVI	Alfentanil CSCI or CIVI	15:1	Divide 24hour morphine dose by 15	Morphine CSCI 30mg/24hours ÷ 15 = alfentanil CSCI 2mg/24hours
Morphine CSCI or CIVI	Diamorphine CSCI or CIVI	2:1	Divide 24hour morphine dose by 2	Morphine CSCI 15mg/24hours ÷ 2 = diamorphine CSCI 7.5mg/24hours
Morphine CSCI or CIVI	Fentanyl CSCI or CIVI	50:1 <sup>30</sup>	Divide 24hour morphine dose by 50 to give fentanyl dose in <i>mg/24hours</i>  <i>Then</i> multiply fentanyl dose in <i>mg/24hours</i> by 1000 to convert to <i>micrograms/24hours</i>	Morphine CIVI 25mg/24hours ÷ 50 = fentanyl CIVI 0.5mg/24hours  Fentanyl CIVI 0.5mg/24hours x 1000 = 500micrograms/24hours
Morphine CSCI or CIVI	Fentanyl patch	50:1	Divide 24hour morphine dose by 50 to give fentanyl dose in <i>mg/24hours</i>  <i>Then</i> multiply fentanyl dose in <i>mg/24hours</i> by 1000 to convert to <i>micrograms/24hours</i>  <i>Then</i> divide by 24 to convert to <i>micrograms/hour</i>	Morphine CSCI 30mg/24hours ÷ 50 = fentanyl transdermal 0.6mg/24hours  Fentanyl 0.6mg/24hours x 1000 = 600micrograms/24hours  Fentanyl CIVI 600micrograms/24hours ÷ 24 = 25micrograms/hour patch
Morphine CSCI or CIVI	Hydromorphone CSCI or CIVI	5:1	Divide 24hour morphine dose by 5	Morphine CSCI 25mg ÷ 5 Hydromorphone CSCI =5mg
Morphine CSCI or CIVI	Oxycodone CSCI or CIVI	1:1	Use the same dose	Morphine CSCI 50mg/24h = oxycodone CSCI 50mg/24hours

<sup>30</sup> Some centres use equianalgesic ratio of 75:1 depending on circumstances

## Change of route

Conversion		Ratio	Calculation	Example
From	To			
Buprenorphine sublingual	Buprenorphine IV or SC <i>bolus</i>	2:1	Divide sublingual buprenorphine by 2	Buprenorphine SL 200micrograms ÷ 2 = buprenorphine SC bolus 100micrograms
Diamorphine intranasal	Diamorphine IV or SC bolus	2:1	Divide intranasal diamorphine by 2	Diamorphine intranasal 2mg ÷ 2 = Diamorphine intravenous 1mg
Hydromorphone oral	Hydromorphone CSCI or CIVI	2:1 <sup>31</sup>	Divide 24hour hydromorphone dose by 2	Hydromorphone oral 10mg ÷ 2 = hydromorphone CSCI 5mg
Morphine oral	Morphine CSCI or CIVI	3:1	Divide 24hour morphine oral dose by 3	Morphine oral 15mg ÷ 3 = morphine CSCI 5mg
Methadone oral	Methadone CIVI or CSCI	2:1	Divide 24hour methadone dose by 2	Methadone oral 2mg ÷ 2 = methadone CSCI 1mg
Oxycodone oral single dose	Oxycodone SC or IV bolus single dose	1.5:1	Divide oxycodone oral dose by 1.5	Oxycodone oral 4.5mg ÷ 1.5 = oxycodone IV/SC bolus 3mg
Oxycodone oral	Oxycodone CSCI or CIVI	1:5:1 <sup>32</sup>	Divide 24hour dose of oral oxycodone by 1.5	Oxycodone oral 90mg/24hours ÷ 1.5 = oxycodone CSCI 60mg/24hours
Tramadol oral	Tramadol CIVI or CSCI	1:1	Use the same dose	Tramadol oral 10mg/24hours = tramadol CSCI 10mg/24hours

<sup>31</sup> Some centres use equianalgesic ratio of 3:1 depending on circumstances

<sup>32</sup> Some centres use a equianalgesic ratio of 2:1 for infusions

## Appendix 2: Opioid stewardship

- Opioids are high-risk medicines which are widely used in the field of paediatric palliative care. The concept of opioid stewardship is based on the principles of antibiotic stewardship in that opioids should be used for the right patient in the right way at the right time. Recent evidence shows an increasing trend in global opiate use which has seen a corresponding increase in harm. Opioid stewardship entails a set of systematic and coordinated interventions designed to improve the health of and minimise harm to our patients.
- Key aspects to opiate stewardship that should be followed include:
  - Patient information gathering and shared decision making
  - Effective communication with the patient or their proxy and between members of the multidisciplinary team
  - Thorough assessment and regular re-assessment of the indication(s) for opioid therapy
  - Risk-benefit analysis
  - Appropriate prescribing and dispensing, ideally by a single prescribing team.
  - Monitoring and management of opioid adverse effects
  - Clear documentation
  - Regular review of therapy
  - Appropriate storage
  - Disposal of unused opioids

## Appendix 3: Prolonged QT syndrome

- Polypharmacy in paediatric palliative care is common. Therefore prescribers must be aware of potential risks, including prolongation of the QT-interval. This is particularly relevant to paediatric patients receiving palliative care where there may be additional risk factors for prolonged QTc including cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Although the frequency of serious life-threatening arrhythmias, including Torsades de pointes (TdP), in this population appears to be low, it should be considered carefully when prescribing medications known to prolong QTc.

### Drugs associated with prolonged QT-interval

- Drugs that may affect the QT-interval can be subdivided into four categories
  1. Known risk of serious life-threatening arrhythmias -These drugs prolong the QT-interval AND are clearly associated with a known risk of TdP, even when taken as recommended.
  2. Possible risk of TdP-These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.
  3. Conditional risk of TdP-These drugs are associated with TdP BUT only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalaemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).
  4. Drugs to avoid in congenital long QT syndrome (cLQTS)-These drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories PLUS additional drugs that do not prolong the QT-interval per se but which have a special risk because of their other actions.
- Drugs in group 1, (as of July 2023) *but not those in the other categories* are identified in the notes section of the relevant monograph in the formulary. However the list of drugs associated with prolonged QT-interval is being continually updated. Professionals are strongly advised to check the most up to date list on <https://www.crediblemeds.org/> when prescribing or advising on prescribing for patients at increased risk of prolonged QT-interval

### Safe prescribing

- When prescribing drugs which are known to prolong the QT-interval it is important to gather information about any additional risk factors in order to make an informed decision about the risks and benefits of the proposed drug.
- Co-administration of two or more drugs that prolong the QTc should be avoided where possible.
- For high risk patients consider a 12 lead ECG before starting treatment and repeating once the medication has reached steady state.

## Appendix 4: Benzodiazepines

### Approximate equivalent oral anxiolytic sedative doses<sup>33/34</sup>

Benzodiazepine	Approximate equivalent oral dose
Clobazam	10mg
Clonazepam	250micrograms
Diazepam	5mg
Lorazepam	500micrograms
Midazolam	2.5mg <sup>b</sup> <i>intravenous or subcutaneous</i>
Temazepam	10mg

### Comparative pharmacokinetic data

#### Diazepam<sup>a</sup>

	Bioavailability	Onset of action (minutes)	Time to peak plasma concentration (minutes)	Duration of action (hours)	Half-life (hours) (including active metabolites)
<b>Diazepam oral</b>	>90%	15-30 <sup>35</sup> 30-90	30-90	3-30	25-50 20-100 <sup>c</sup>
<b>Diazepam intravenous</b>		1-5	≤15 (oil) ≥15 (emulsion)	15-60	
<b>Diazepam rectal</b>	65-85% 90% <sup>c</sup>	<30	10-30 <sup>c</sup> <30		

<sup>33</sup> BNF 85: March-September 2023. London: Pharmaceutical Press; 2023.

<sup>34</sup> Charlesworth S, Howard P, Wilcock A, editors. PCF8: palliative care formulary. Eighth edition. London: Pharmaceutical Press; 2022.

<sup>35</sup> Medicines for Children 2003

**Lorazepam**<sup>36</sup>

	Bioavailability	Onset of action (minutes)	Time to peak plasma concentration (minutes)	Duration of action (hours)	Half-life (hours) (including active metabolites)
Lorazepam sublingual		5	150		
Lorazepam oral	90% <sup>a,37</sup>	10-15	150 120 <sup>b</sup>	6-72 8 <sup>b</sup>	10-20 <sup>a,b</sup>
Lorazepam intravenous		2-5 <sup>b</sup> 10		4-6 <sup>b</sup>	12-16

**Midazolam**<sup>a,b</sup>

	Bioavailability	Onset of action (minutes)	Time to peak plasma concentration (minutes)	Duration of action (hours)	Half-life (hours) (including active metabolites)
Midazolam buccal	85% 75% <sup>38</sup>	15 5 <sup>b</sup>	≤30		
Midazolam oral	40%	20-30 10-30 <sup>b</sup>	30-60	<4 20-90 <sup>3</sup> minutes	1-4 2-5 <sup>a,b</sup>
Midazolam Sub-cutaneous	95%	5-10	30		
Midazolam intravenous		2-3 <sup>a,b</sup>		30-60mins <sup>b</sup>	

<sup>36</sup> Charlesworth S, Howard P, Wilcock A, editors. PCF8: palliative care formulary. Eighth edition. London: Pharmaceutical Press; 2022

<sup>37</sup> Medicines for Children 2003

<sup>38</sup> Kienitz R et al. Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 2022 Sep;36(9):951–75.

## Appendix 5: Gabapentin to pregabalin switch

- Gabapentin and pregabalin have similar mechanisms of action. However, gabapentin absorption is saturable, leading to non-linear pharmacokinetics, whereas pregabalin possesses linear pharmacokinetics. Furthermore, clearance of pregabalin is faster in children under 30 kg and particularly those under 6 years of age. Higher doses and/or more frequent dosing interval may therefore be needed. As a consequence, switching between gabapentin and pregabalin is not straight-forward.
- There is limited evidence in the literature with regard to managing a switch, with no evidence in children. However many pain centres in the UK have developed local protocols for a switch in adults, with no reports of adverse effects. The following conversion factors have been used:
  - 1/6 is generally accepted as a standard conversion however a range of factors from 1/4 to 1/9 have been used to accommodate practical dosing schedules
  - Lower conversion factors of 1/6 to 1/9 used for higher gabapentin dosing to accommodate the non-linear kinetics of gabapentin
- The table below details a switch from gabapentin to pregabalin for neuropathic pain in children extrapolated from available adult data. Conversion factors allow for practical dosing.

**Table 2: Gabapentin to Pregabalin switch**

Age	Gabapentin APPM formulary dose	Recommended conversion ratio <sup>39</sup>	Pregabalin APPM formulary dose	Recommended initial maximum pregabalin dose
<b>1-23 months</b>	5-10mg/kg/dose 3 times daily	1/6	1-5mg/kg/dose 2 times daily	5mg/kg/dose 2 times daily
<b>2-11 years</b>	5-30mg/kg/dose 3 times daily	1/6	1-5mg/kg/dose 2 times daily	5mg/kg/dose <sup>40</sup> 2 times daily Maximum 100mg/dose
<b>12 years and over</b>	300mg 3 times daily	1/5	<b>12-15 years</b> 1-5mg/kg/dose 2 times daily	100mg 2 times daily
	400mg 3 times daily	1/6		100mg 2 times daily

<sup>39</sup> From adult literature and taking into account recommended doses of gabapentin and pregabalin in neonates and children

<sup>40</sup> Children with body-weight less than 30Kg and especially those under 6 years may require up to 15mg/kg/24hours, giving a conversion ratio that may be as much as 1/3



	600mg-1.2g 3 times daily	1/6-1/9	<b>16 years and over</b> 75mg-300mg 2 times daily	200mg 2 times daily
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Using the table:

1. Calculate the child's total daily gabapentin dose in mg/24hours
2. Multiply by the relevant conversion ratio to get the approximate equivalent dose of pregabalin in mg/24hours. Divide the total daily dose of pregabalin by two for twice daily administration
3. The dose of pregabalin would be expected to fall within the range given in the formulary and should not exceed the recommended initial maximum dose

## Appendix 6: Buccal administration of liquid preparations

- Buccal or sublingual administration is increasingly accepted as a convenient, painless method of drug delivery. Potential advantages of administration by these routes include rapid absorption without the need to swallow and by-passing first pass metabolism. Absorption of drugs via the buccal or sublingual routes is influenced by a number of important factors with the potential for differences in bioavailability between patients and in the same patient over time.
- Factors affecting absorption via buccal or sublingual routes
  - Volume of the oral cavity
  - pH of the oral cavity
  - Rate of saliva production
  - Site of drug delivery: the sublingual mucosa has higher permeability than the buccal mucosa but small volume for administration
  - Relative lipophilic (transcellular absorption) versus hydrophilic (paracellular absorption) properties of the molecule
  - Molecular size: molecules (molecules greater than 500 Da are unlikely to be absorbed)
  - Excipients
  - Volume of administration
  - Ability to swallow or co-operate with not swallowing
  - Palatability
- The volume of liquid preparation that can be tolerated in the buccal or sublingual cavity without swallowing has been estimated as 2ml in adult patients. No equivalent data exists for children and extrapolating to the paediatric population is complex. The table below provides approximations based on scaling by weight, body surface area and head circumference. In general liquid preparations for buccal or sublingual administration should be administered in the smallest measurable volume

Age range	Estimated maximum volume for buccal or sublingual administration
Neonate -11 months	0.5ml
1-5 years	1ml
6-10 years	1.5ml
11 years and over	2ml

## Appendix 7: Dosing in obesity

- Patients requiring paediatric palliative care are frequently atypical in terms of weight for age or body composition. Childhood obesity, defined as body weight greater than or equal to the 98<sup>th</sup> centile for age, is increasing. Even patients who are seemingly a normal weight for age may have relatively more body fat and less lean muscle mass if they are almost completely and permanently immobile and non weight-bearing.
- Children are usually dosed according to their body-weight or age, as a surrogate of 'normal' size and function. However, in children with obesity there is a risk of drug overdose if total body weight is used. Therefore, for a small selection of drugs it is recommended to use either ideal body weight (IBW) or adjusted body weight (AdjBW))

Weight (kg)	Definition
Total Body Weight (TBW)	Weight in kg (no adjustment necessary)
Ideal Body Weight (IBW)	Cross reference height centile to weight for that centile  If height is not available, use length or arm span.
Adjusted Body Weight (AdjBW)	$IBW + \text{Adjustment Factor } (0.3) \times (TBW - IBW)$

### Analgesics

- Fentanyl (AdjBW)
- Ibuprofen (AdjBW)
- Morphine (IBW)
- Paracetamol (AdjBW)

### Anticonvulsants

- Carbamazepine (IBW)
- Levetiracetam (maintenance) (AdjBW)
- Phenytoin (maintenance) (AdjBW)

## Appendix 8: Protocol for Subcutaneous Drug Administration

In palliative care the sub-cutaneous route of drug administration is often the most convenient. It has many advantages, including being seen as less invasive than intravenous therapy, not requiring venous access where such access may be difficult or impossible, being easily monitored for local irritation, and being easily relocated if such problems occur.

The network of small blood vessels provide good absorption of medication and parenteral drugs are often absorbed more rapidly than oral drugs. The sub-cutaneous tissue lies between the skin and the underlying muscle, it is made up of loose connective tissue and varying amounts of fat. It also contains cutaneous nerves, small lymph vessels and blood vessels.

It is also widely acceptable in the community setting, making it possible to manage patients at home when more invasive devices would preclude this.

Sub-cut treatment can be given when it is not possible or desirable for it to be given orally.

Indications for its use may be:

- Persistent nausea and vomiting.
- Dysphagia.
- Mouth/throat/oesophageal lesions.
- Intestinal obstructions.
- Malabsorption of oral medication.
- Unconscious child/young person.
- Profound weakness when child/young person unable to swallow medication.

Advantages to this method of administration are:

- Constant serum plasma levels ensuring better pain control.
- Usually reloaded once every 24 hours.
- No repeated injections.
- Permits better control of nausea and vomiting.
- Control of multiple symptoms with a combination of drugs.

If possible, involve the child or young person in the choice of site. This may increase compliance and acceptability.

The most frequently used sites are:

- Abdomen or chest wall.
- Thighs; upper and lateral aspects.
- Buttocks.
- Upper arms.

Preparation of child and family

- Explain the full procedure to the child and family including the purpose and any possible side effects and allow them to ask questions.
- Assess the child for the most suitable infusion site.
- Offer topical anaesthetic. EMLA or Ametop.
- Apply topical anaesthetic cream according to manufacturers' instructions and allow maximum time for it to take effect.
- If possible, involve the parents, particularly if the treatment is being given at home. This will offer security to the child and assist with distraction.

#### Preparation of medication and equipment

- Check the prescription is written correctly to comply with local policy.
- Check child/young person's allergies.
- Wash hands according to standard (universal) precautions to reduce the risk of cross infection.
- Prepare a tray or suitable working surface.

#### Equipment required

- Syringe driver policy.
- Syringe driver that has been serviced in the last 12 months.
- Medication to be administered.
- Luer lock syringe appropriate to the infusion volume, usually 10 or 20ml.
- Needles for drawing up the medication.
- Butterfly needle appropriately sized depending on age/size of child/young person and amount of sub-cutaneous tissue they have.
- Opsite or tegaderm dressing to secure butterfly.
- Portable syringe pump. Graseby MS26, Mckinley T34 or BD BodyGuard
- Sharps bin to ensure equipment is disposed of safely.
- Prepare the drug and diluents, checking name, dose, and expiry date.
- Draw up the injection with the needle and luer lock syringe.
- Remove needle and discard in sharps bin.
- Complete label to attach to syringe with drug name(s), strength, batch number, child/young person's name, and date of birth and initialled by two nurses.
- Connect the syringe to the extension set and prime line and butterfly needle. Ensure medication at tip of needle.

#### Administration

- Remove anaesthetic cream 2-5 minutes before needle insertion to allow skin to dry and to maximise its effect.
- Check child/young person's details with parents and second nurse.
- Ensure the child is comfortable and if appropriate, encourage them to participate. This may help the child to co-operate and ensure their safety.
- Wash hands.

- Lift a skin fold and insert the needle into the sub-cutaneous tissue at approximately a 45-degree angle.
- Ensure the butterfly needle and extension line are connected to the syringe and the syringe is fitted into the pump correctly.
- Start infusion ensuring rate corresponds to prescription.

## Graseby MS26

- Insert 9-volt battery into pump and listen for alarm. Press and hold start/test button for 10 seconds; the motor will then run and stop. Release the button. Observe for the flashing light.
- Ensure you have protective plastic cover for pump.
- Ensure you have a rate adjuster and a Graseby ruler to measure length of syringe contents.
- Wash hands.
- Draw up the prescribed medication and the diluents and make up to **48mm** within the syringe barrel. Check the solution for clouding or crystallisation. If this occurs, do not use and check with pharmacist regarding compatibility of drugs. Whatever syringe size used the total volume should measure **48mm**.
- Connect syringe to butterfly tubing. Prime the line and the butterfly with the prescribed medication. ***Do not prime the line when attached to the child / young person.***
- By loading the syringe and then priming the infusion line it is recognised that this will reduce the duration of the infusion by approximately 2 - 4 hours.

This will occur each time a new infusion line is primed, i.e., on each re-siting of the needle.

Do not make up the fluid lost in the infusion line as this will dilute the drug concentration and thus reduce the amount of medication the child/young person receives each hour.

NB. If the combination of drugs is changed it is essential to replace the infusion line. This prevents a delay in the child or young person receiving the new prescription and possible drug incompatibility occurring in the infusion line.

Hold the syringe driver with the battery side facing you. Press the square actuator button to move the actuator to the far-right hand side. Put the syringe on top of the driver with the barrel in the shallow V shaped recess. The finger grip on the syringe barrel must be in the slot in the case.

Move the actuator up to the syringe plunger by pressing and holding in the button on the side and sliding it along. The push button on the plunger of the syringe must be fitted in the slot in the actuator. Be careful not to push the plunger forwards.

Put the rubber securing strap over the syringe barrel and pull it tight. Hook and then press it into the groove in the side of the case.

Slide the syringe driver into the clear plastic cover with the front facing the side of the cover with the hole in it. NEVER PUT THE SYRINGE DRIVER IN FACING THE OTHER WAY.

### Setting the correct rate for the MS26 and starting the infusion:

- Fill the syringe with the required volume of medication.
- Connect and fill the infusion line. Make sure the connection is secure and the air is expelled.
- Measure the distance in millimetres (mm) from the empty line on the syringes scale up to the line where the plunger piston is.
- In the hospice we draw up 8ml of medication and diluents which runs at 48mm in 24 hours.
- Press and hold the **START** button. The motor will turn and stop after 10 seconds, then the alarm will sound. This will continue for about 15 seconds longer if the button is not released.
- Releasing the button starts the syringe driver. The indicator lamp will begin to flash once every 25 seconds.

### During the administration

It is recommended that procedures are established for regular checks on the progress of the administration. In the hospice or hospital environment this should be done hourly. In a patient home it should be done twice in 24 hours. Parents or carers can be made aware of a few simple checks that can be made:

- The volume is being delivered as expected
- The rate set is the correct value
- The indicator lamp is flashing
- The syringe driver is in good condition.

A family must know who to contact in an emergency.

### Stopping the syringe driver

- When the syringe is empty the syringe driver will stop automatically, and the alarm will sound for about 15 seconds.
- There is no OFF switch to stop the driver before the syringe is empty. To stop it move the rate switches to **00**, the indicator lamp will still flash, or take the battery out.

### Alarms

The syringe driver will give an audible alarm lasting about 15 seconds:

- When a battery is put in.
- When the **START/TEST** button is pressed for longer than 10 seconds.
- When the syringe is empty.
- When the syringe driver has stopped. This may be caused by a blocked or trapped infusion line.

The indicator lamp will stop flashing:

- When the syringe driver has stopped and switched off.
- When the battery needs replacing.

## Troubleshooting

The syringe driver will not start:

- The START button has not been pressed in enough. Press again.
- There is no battery. Fit a battery.
- The battery is in the wrong way round. Refit battery.
- The battery is exhausted. Fit a new battery.
- The syringe driver is faulty. Service needed.

The infusion is going too quickly or has ended early:

- Wrong rate set. Correct error.
- Wrong syringe brand or size. Correct error.
- Syringe plunger push-button or finger grips were not held in the actuator or case correctly. Correct error.
- Plunger position measured wrongly. Correct error.
- Line was filled after the plunger position was measured. Correct error.
- Syringe driver has got wet. Remove from use immediately.

The infusion is going too slowly:

- Wrong rate set. Correct error.
- Wrong syringe brand or size. Correct error.
- Plunger position measured wrongly. Correct error.

The syringe driver has stopped before emptying the syringe:

- Exhausted battery. Fit new battery.
- Blocked or trapped infusion line. Clear line.

The syringe driver has stopped with the lamp still flashing:

- The mechanism for pushing the plunger has worn out. Listen for a faint click when the motor turns a few times. Service needed.



## McKinley T34 Pump 2<sup>nd</sup> edition

### Batteries

Always use a 9-volt battery. When setting up the pump always check there is enough charge in the battery to cover the infusion being set up. To do so follow this procedure:

- Switch the pump ON.
- Press INFO key.
- Select BATTERY LIFE from the menu and press YES to confirm.
- Verify sufficient battery charge is available to complete the current programme. If not, change the battery.

### Program lock

Always use the program lock when the pump is used in a home environment to prevent patient or family changing the prescription.

### Keypad lock

To activate the keypad lock:

- With the pump infusing, press and hold the INFO key until a chart is displayed showing a bar moving from left to right.
- Hold the key until the bar has moved completely across the screen and a beep is heard to confirm the lock has been activated.
- To turn off repeat this procedure. The bar will now move from right (ON) to left (OFF) and a beep will be heard to confirm.

### Infusion set up and programming

- Always use luer lock syringes.
- Priming the infusion set
- After filling the syringe attach the infusion set, prime manually to remove all air from the syringe and extension set and apply clamp to the line.

### Pre-loading and syringe placement

- Before placing the syringe into the pump ensure the barrel clamp arm is down then press and hold the ON/OFF key until the SELF TEST screen appears. Do not label the syringe or apply anything that changes its external diameter at the point where the barrel clamp is applied as incorrect syringe recognition may result.
- Check the remaining battery life is sufficient to cover the infusion you are about to program. Press the INFO key and use the UP or DOWN arrow keys to select battery level. Press YES/START to confirm and view battery status.
- Load the syringe into the pump prior to connecting the syringe to the child/young person.

- The LCD display will show PRE-LOADING and the actuator will start to move. Wait until it stops moving and the syringe detection screen appears.
- If the actuator is not in the correct position to accommodate the syringe leave the barrel arm clamp down and use the FF or BACK buttons on the keypad to move the actuator to the required position. Forward movement of the actuator is limited, therefore repeated presses of the FF key may be required when moving the actuator forward. Backwards movement is not restricted.
- Lift the barrel arm clamp and load the syringe into the pump. Note that the syringe graphic on the screen flashes in three places, the barrel, ear/collar, and plunger, denoting the position and status of each sensor. Seat the collar/ear and plunger first. As you correctly seat each point of the syringe note that the flashing indicator for that sensor becomes solid on the display.
- Lower the barrel arm clamp. If the syringe is correctly loaded the syringe graphic will become solid (no flashing components) and the pump will display the next screen – Size and brand of the syringe detected.

## Syringe Detection and confirmation

- Check the LCD display to ensure the pump has correctly identified the syringe size and brand. If it is not correct use the UP or DOWN arrow keys to scroll between brands.
- Press YES/START to confirm.
- If the pump was stopped and turned off before the last program reached End Program, the Resume prompt screen will appear. Press NO to continue programming the new regime.
- Once the syringe brand and size are confirmed the pump calculates and displays the deliverable volume in the syringe.
- The pump cannot deliver the full contents of all syringe brands/sizes so in some cases there may be a slight residual volume left in the pump when the actuator has travelled to the zero position. So, when the syringe is loaded, the VTBI may read 17.5ml when 18ml has been drawn up.
- Press YES/START key to confirm the volume to be infused (VTBI).
- Set duration of infusion. Will read 24:00. Use UP and DOWN arrow keys to set desired duration or press YES to confirm 24:00.

## Setting the Infusion Rate

- The pump calculates and displays the rate (in millilitres per hour) required to deliver the VTBI over the infusion duration confirmed.
- Press YES to confirm the calculated rate or use the UP and DOWN arrow to adjust. Changing the rate will alter the duration confirmed at the previous step.

## Starting the infusion

- The summary screen confirms the volume to be infused, duration and infusion rate. **You must always check the details on this screen match the prescription.**
- Press YES/START to confirm the infusion parameters.

- Pump prompts, START INFUSION? Check infusion set is attached to patient access device and the clamp is released. Press YES/START to commence infusion.
- While running, the LCD displays infusion 'Time Remaining' (top line), 'Infusion Rate' (in bold on the middle line) and the bottom line will alternate between 'syringe size and brand' and 'Pump Delivering.'

### Recommended checks during infusion

- CHECK THE LCD DISPLAY to confirm the pump is still running at the same infusion rate as originally set (unless the titration option has been enabled and the user has been authorised to adjust the rate within the programmed limits.
- CHECK THE GREEN LED IS FLASHING AND/OR pump delivering animation appears intermittently on the bottom line of the LCD display.
- CHECK FOR SIGNS OF PHYSICAL DAMAGE to the pump or accessories.
- PRESS THE INFO KEY TO CHECK:
- **Single Press:** Volume to be infused (VTBI) & Volume Infused (VI).
- **Double Press:** for battery life remaining.

This information is for a quick reference only. You must refer to the pump manufacturer's booklet for the full information and instructions.

### T34 3<sup>rd</sup> Edition

Different to 2<sup>nd</sup> edition as has universal symbols on keypad and no text.  
Otherwise, use is the same

### BD BodyGuard T

The company recommend the use of Duracell Plus, Duracell Ultra or Varta Power One batteries  
The pump is used in the same way as the T34 3rd Edition  
Keypad is the same



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