Basic Symptom Control in Paediatric Palliative Care

2022

10th Edition

Published by Together for Short Lives

Editor in Chief

Dr Satbir Singh Jassal MBE
Medical Director Paediatric Palliative Medicine
Loughborough

Contributions from

Dr Ella Aidoo
Consultant in Paediatric Palliaitive Medicine
Evelina Children's Hospital
London

Dr Anna-Karenia Anderson
Consultant in Paediatric Palliative Medicine
The Royal Marsden NHS Foundation Trust, London
Shooting Star Children's Hospice, Surrey

Dr Lynda Brook
Macmillan Consultant in Paediatric Palliative Care
Alder Hey Children's Hospital Specialist Palliative Care Team
Liverpool

Dr Finella Craig
Consultant in Paediatric Palliative Medicine
Great Ormond Street Children's Hospital/ Institute of Child Health
London

Dr Charlotte Burleigh
ST5 Paediatrics
Bradford Teaching Hospitals NHS Trust
Bradford

Lynne de Melo
Clinical Nurse Specialist
Rainbows Hospice for Children and Young People
Loughborough

Dr Jonathan Downie
Consultant in Paediatric Palliative Medicine
Royal Hospital for Children
Glasgow

Prof Julia Downing
Chief Executive
International Children's Palliative Care Network

Francis Edwards
Lead Nurse for Paediatric Palliative Care & Bereavement Support (Retired)
Bristol Children's Hospital
Bristol

Dr Jo Griffiths
Consultant in Paediatric Palliative Medicine & Community Child Health
All Wales managed clinical network & Swansea Bay University Health Board
Wales

Dr Philippa Grainger
SpR in Paediatrics,
Children's Hospital, Cardiff and Vale UHB
Cardiff

Dr Clare Hale
Deputy Medical Director Paediatric Palliative Medicine
Loughborough

Dr Anne Marie Harris
ST6 Paediatric Registrar, Paediatric Supportive and Palliative Care team
Royal Hospital for Children
Glasgow

Dr Richard D. W. Hain
Consultant and Clinical Lead, All Wales Paediatric Palliative Care Network
Honorary Professor in Clinical Ethics, College of Human and Health Sciences, University of Swansea
Tŷ Hafan Children's Hospice Hayes Road Sully
Wales

Dr Rachel Haplin-Evans
Consultant in Paediatric Palliaitive Medicine
Perth Children's Hospital
Western Australia

Dr Emily Harrop
Consultant in Paediatric Palliative Care
Oxford University Hospital NHS Trust
Helen and Douglas House
Oxford

Dr Sarina Jassal
ST2 Paediatrics
Leeds Teaching Hospitals NHS Trust
Leeds

Helen Kenney
Respiratory Nurse Specialist
Leicester Royal Infirmary
Leicester

Dr Joanna Laddie
Consultant in Paediatric Palliative Medicine
Evelina London Children's Hospital
London

Jayne Lewis
Community Children's Dietitian
Home Enteral Feeding
East Oxford Health Centre
Oxford

Dr Susie Lapwood
Senior Associate Specialist Emeritus
Helen and Douglas House Hospice Care for Children
Oxford

Dr Yifan Liang
Consultant in Paediatric Palliative Medicine
Birmingham Women's and Children's and Community Healthcare Trusts
Birmingham

Dr Daniel E Lumsden
Consultant Paediatric Neurologist
Evelina London Children's Hospital
London

Dr Renee McCulloch
Consultant in Paediatric Palliative Medicine
Great Ormond Street Children's Hospital/ Institute of Child Health
London

Dr Dilini Rajapakse
Consultant in Paediatric Palliative Medicine
Great Ormond Street Children's Hospital/ Institute of Child Health
London

Dr Kate Renton
Consultant in Paediatric Palliative Medicine
University Hospital Southampton / Naomi House Hospice
Southamptom

Dr Ross Smith
Consultant in Paediatric Palliative Medicine
Leeds Teaching Hospital NHS Trust / Martin House Children's Hospice
Leeds

Dr Archana Soman
Consultant in Paediatric Palliative Care
Sheffield Children's Hospital / Bluebell Wood Children's Hospice
Sheffield

Dr Chakrapani Vasudevan
Consultant Neonatologist
Bradford Teaching Hospitals NHS Foundation Trust
Bradford

Dr Timothy Warlow
Consultant in Paediatric Palliative Medicine
University Hospitals Southampton & Wessex Children's Hospice Trust
Southampton

Proofreaders

Lizzie Chambers
Director of Programmes & Professional Engagement
Together for Short Lives
UK

Dr Clare Hale
Deputy Medical Director Paediatric Palliative Medicine
Loughborough

Dr Susie Lapwood
Senior Associate Specialist Emeritus
Helen and Douglas House Hospice Care for Children
Oxford

Table of Contents

Foreword

The Basic Symptom Control Manual, now in its 10th 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 later in 2022.

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

Chair, Together for Short Lives

Indroduction

Welcome to the 10th 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 uract 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 enteraly 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.

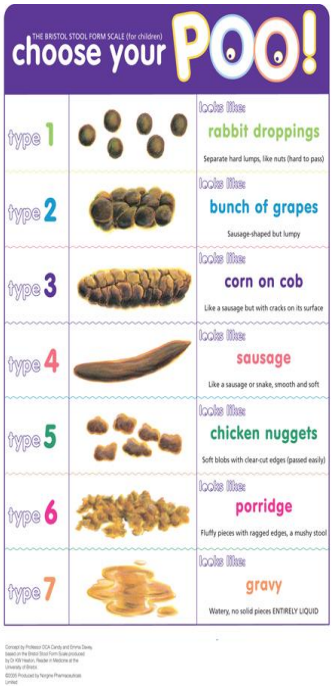
- Investigation and referrals to other services may be appropriate in refractory constipation for consideration of uncommon complications.

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
Osmotic laxatives: (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 first line in managing constipation.
Lactulose	Draws fluid from the body into the bowel.	Useful as alternative to Movicol in: • children who do not tolerate larger oral fluid volumes • neonates/infants with cardiac conditions
Stool softeners: (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.

Stimulant laxatives: (oral and rectal routes)	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 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 enaema (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 maybe 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 diarrohea. 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 cgent.

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 ileotomy 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. Anticolinergics eg buscopam, 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 outsides 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 them 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[1].

Decision making model
Decision making must be made on the grounds of the **best interests**[2] 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.

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

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[3] 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

[3] Mental Capacity Act 2005 Code of Practice HMSO 2007

(IMCA)[4]. The IMCA will have authority to make enquiries about the patient and contribute to the decision by representing the patient's interests but cannot make a decision on behalf of the patient.

Children and young people who may have capacity

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

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

Children and young people who lack capacity

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

[4] Making Decisions: Office of the Public Guardian Independent Mental Capacity Advocate Service OPG606
[5] 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.[6]

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

The Nuffield Council on Bioethics[7] 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[8].
- 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.

[6] 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*

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

[8] 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.[9]
- 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[10]. 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

[9] General Medical Council. Treatment and Care Towards the End of Life, 2010.
[10] 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[11], 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[12].

Clinically assisted hydration and nutrition

[11] RCPCH Making decisions to limit treatment in children with life threatening and life limiting conditions 2015
[12] 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 [13].

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[14].

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

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

[14] *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 appraised of the treatment options and potential consequences.

Consent to treatment

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

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[15].

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[16].

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[17] (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[18] and Northern Ireland[19], although this has not yet been tested in the courts.

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

[16] Mental Capacity Act 2005 Code of Practice HMSO 2007

[17] 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

[18] 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.

[19] 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[20].

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

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

[20] 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 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.

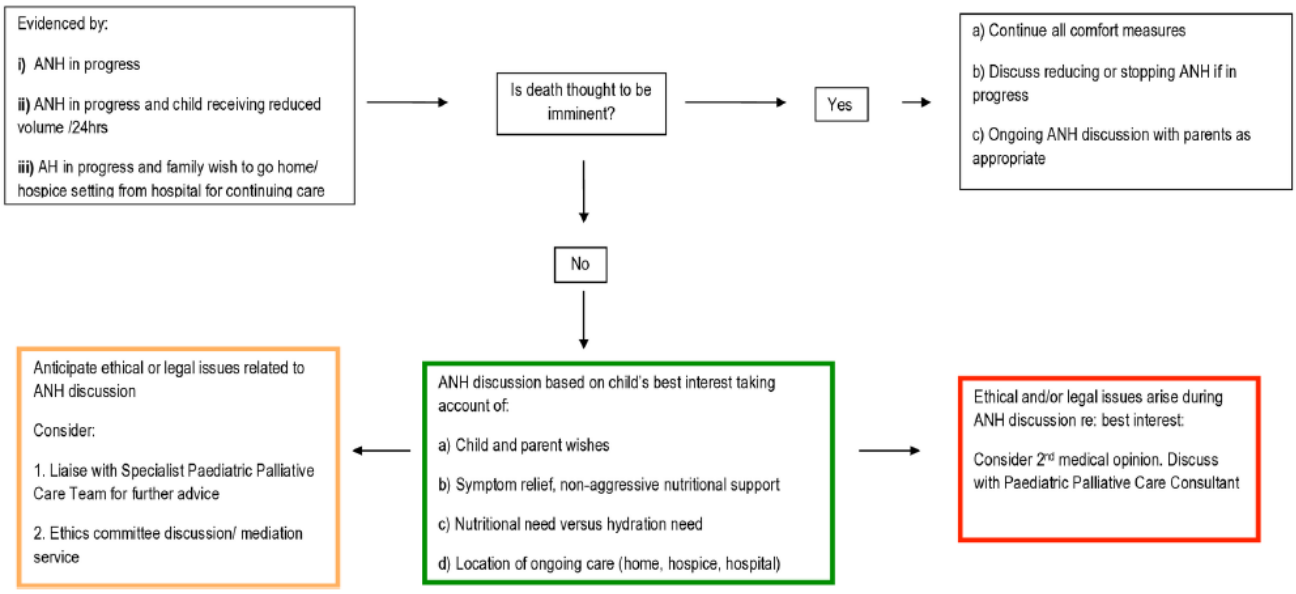
NICE (NG61) made the following recommendation regarding hydration & nutrition at the end of life:

- 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:

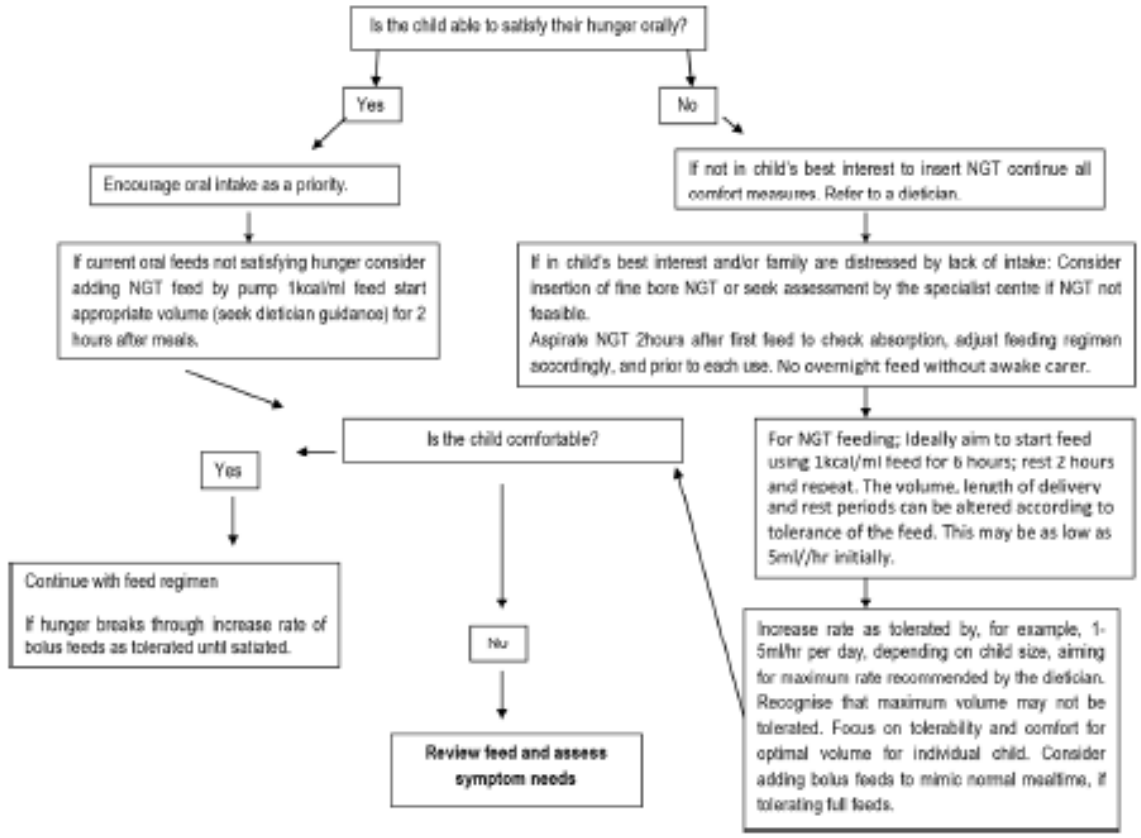


Professional decision-making algorithm for artificial nutrition and hydration (ANH) management

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 that 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=WEaKkI2zzMM.

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 :
- 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:
    - www.gbukenteral.com (Mini buttons)
    - www.vygon.co.uk (Mic-key buttons)
    - www.appliedmedical.net (Bard button)
    - 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 [(5)], 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 [(4)].

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^{rds} of children, with a more slowly progressive disease being seen in 1/3rd 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 case 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 causinges 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 Benzodiazipines 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/mm3
- 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

[138]

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-oesophagel 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 jejeunosomy 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 Jejeunostomy 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:

- 2nd 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

[7, 135, 150-161]

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®, BioXtra® gel and AS Saliva Orthana®.
- Regular lip care with petroleum jelly such as Vaseline® 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.
    - Glycopyronnium 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/ephineprine 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	Moderate	Severe
	(<5%)	(5-10%)	>10%
Decreased urine output	+	+	+
Dry mouth	+/-	+	+
Decreased skin turgor	-	+/-	+
Tachypnoea	-	+/-	+
Tachycardia	-	+/-	+

NB: Tachypnoea may be due to, or worsened by, metabolic acidosis and pyrexia.
Tachycardia may be due to hypovolaemia, but also due to other causes e.g., pyrexia, pain or irritability.
A low blood pressure is a serious sign in a child: it may be due to 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:

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

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.

Category 1	**Life-threatening conditions for which curative treatment may be feasible but can fail** 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. *Examples of conditions: extreme prematurity, congenital heart disease, severe PPHN*
Category 2	**Conditions where premature death is inevitable** 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. *Examples of conditions: chromosomal abnormalities, bilateral renal agenesis*
Category 3	**Progressive conditions without curative treatment options** Treatment is exclusively palliative and may commonly extend over many months or years. *Examples of conditions: spinal muscular atrophy, mitochondrial disorders*
Category 4	**Irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death** *Examples of conditions: severe hypoxic ischaemic encephalopathy*

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 (unlicenced). 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 1st 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 2nd line anticonvulsant. Loading doses typically given IV. Can be given enterally. Can cause skin and blood disorders with prolonged use.
Levetiracetam	Alternative 2nd or 3rd line anticonvulsant. Loading doses typically given IV. Can be given enterally.
Midazolam	2nd or 3rd 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 thought 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.

Antiepileptic drugs

Modified from R. Mattson Epilepsia vol 36, supp 2, 1995 [184], [179]

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

Lamotrigine	Broad spectrum, sense of well being.	Hypersensitivity reaction rash, metabolism inducible. Dizziness, ataxia, somnolence.	
Vigabatrin	Effective in partial and tonic-colonic .seizures, infantile spasms	Eye problems, dyskinesias.	Unique mechanism of action.

Intractable epilepsy

The management of intractable epilepsy[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-oesophogeal 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. hyercalcaemia) – 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	Ondonsetron Haloperidol	As above.
Raised intracranial pressure (Tumour / blocked shunt)	Cyclizine Dexamethasone	Medulla oblongata. As above.
Bowel obstruction	Cyclizine, Hysoscine butylbromide / Octreotide*	As above. Antisecretary antimuscurinic. 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 theirr 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
Face	No expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arches, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	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
Face	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: _____
Legs	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: _____
Activity	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: _____
Cry	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: _____
Consolability	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
Crying Irritability	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)
Behavior	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)
Facial Expression	Mouth is relaxed No expression	Minimal expression with stimuli	No sedation No signs of pain	Any pain expression intermittent	Any pain expression continual
Arms and Legs Tone	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
Vital Signs: Heart Rate, Respiratory Rate, Blood Pressure, Oxygen Saturation (SaO2)	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_2 76-85% with stimuli – quick increase	Increase greater than 20% from baseline SaO_2 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 is 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.

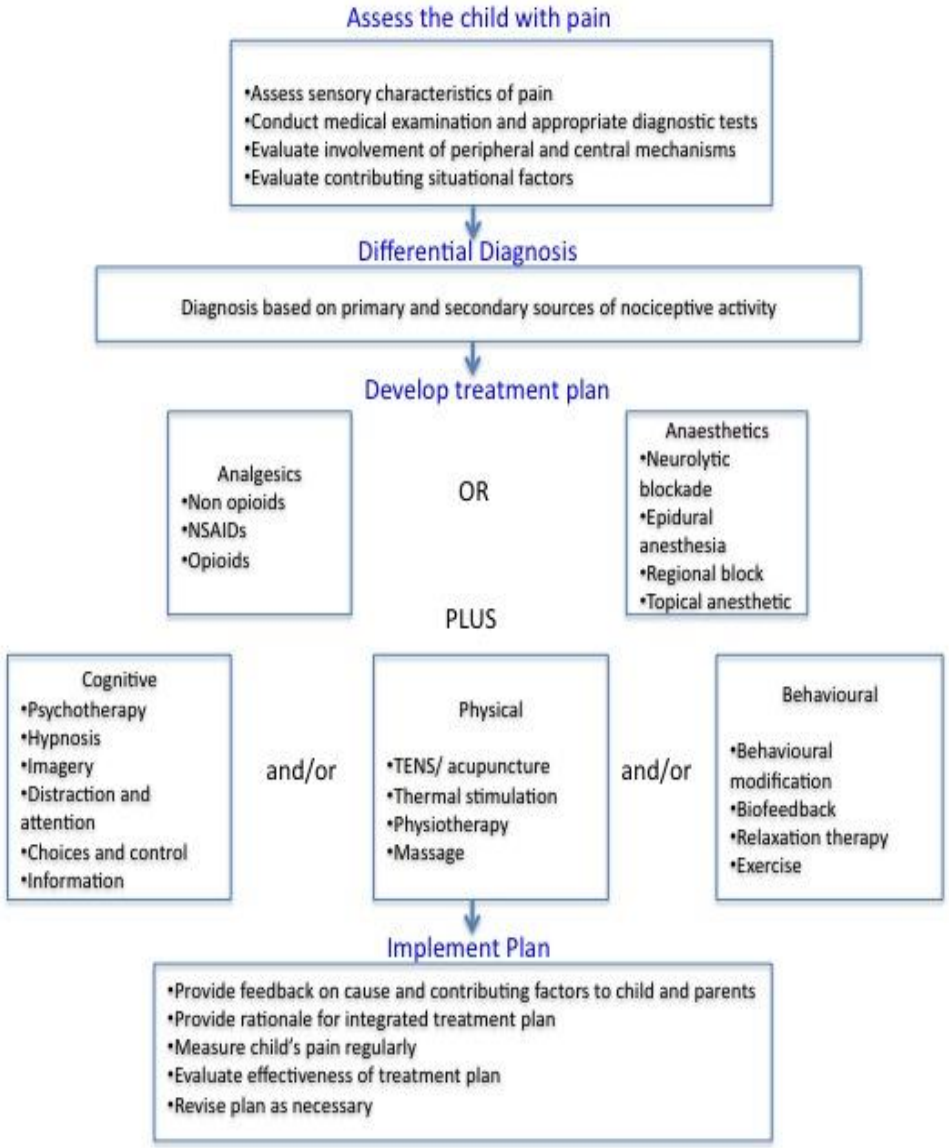
The latest initiative from the World Health Organisation (WHO), 'WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illness' 2012 has taken the best available evidence and developed a new guideline to improve the management of persisting pain in children. Persisting 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").

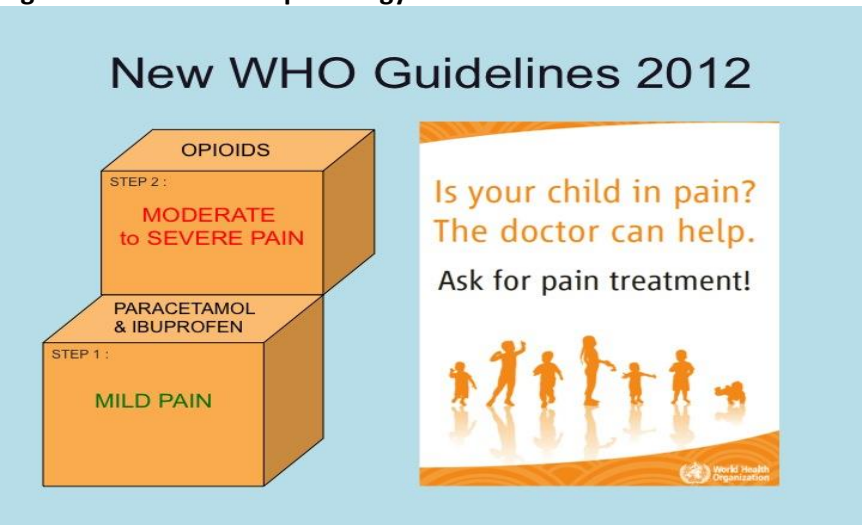
Using a Two-Step Strategy

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 1/5th to 1/10th of the total daily dose, however, historical practice has been based upon adult palliative care prescribing and calculated as 1/6th of the total daily dose of opioid. The benefit of a lower breakthrough dose (1/20th -1/10th) enables closer and probably safer, titration of dosing in children.

Other helpful guidance to prescribing opioids:

- Opioid analgesia must be prescribed on a regular basis when pain is frequent or constant rather than 'as needed'.
- Effective analgesia is achieved through gradual increase in opioid until pain relief is achieved.

- In practice a 4 hourly dosing schedule for immediate release opioid works well, although there is wide inter-individual variability. 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

Figure 3: Opioid Side Effects	
Sedation	One of first side effects to occur in opioid naïve patient or when opioids are significantly increased. May last a few days but then subsides. Warning parents/ carers avoids unnecessary worry.
Constipation	Very common in children. Regular laxatives (stimulant and softener) are required prophylactically. Good evidence in adults that opioid antagonists naloxone and methylnaltrexone are effective in opioid induced constipation without causing opioid withdrawal. Fentanyl has been reported as causing less constipation than other opioids.
Pruritus	Not uncommon in children. Usually occurs around the nose and face.
Nausea	Less common in children than adults but possibly under reported.
Myoclonus	Not infrequent in children and usually prompts opioid switching or dose reduction.
Urinary retention	Seen in children particularly after rapid dose escalation and spinal or epidural opioids. Anecdotally, children seem to experience urinary symptoms (usually hesitancy) 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 heterogenous 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.

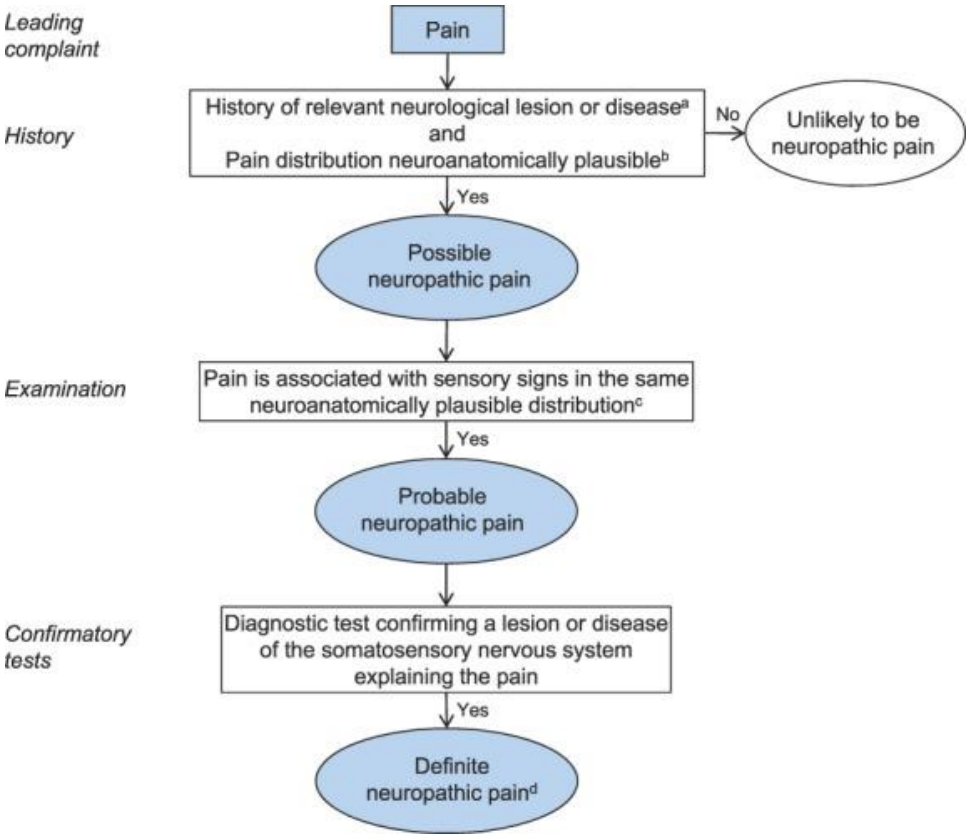
In adult practice assessment and diagnosis is more rigorous, with amongst other things, the presence of pain with a distinct sensory distribution in a corresponding body part, indication of

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 α-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 μ-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.

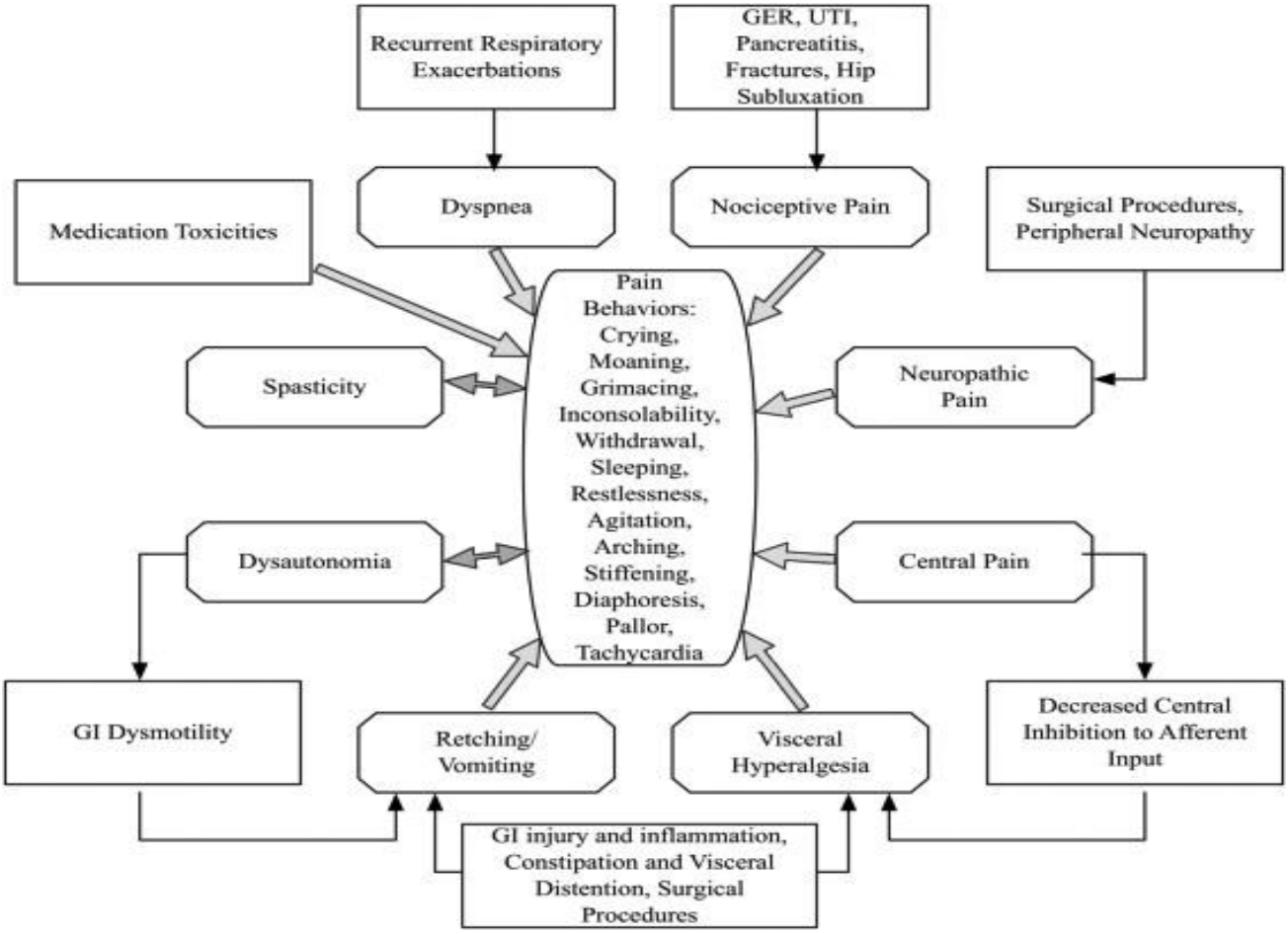


Figure 5: Sources of Pain Behaviours in Children with Severe Neurological Injury (with permission)

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.

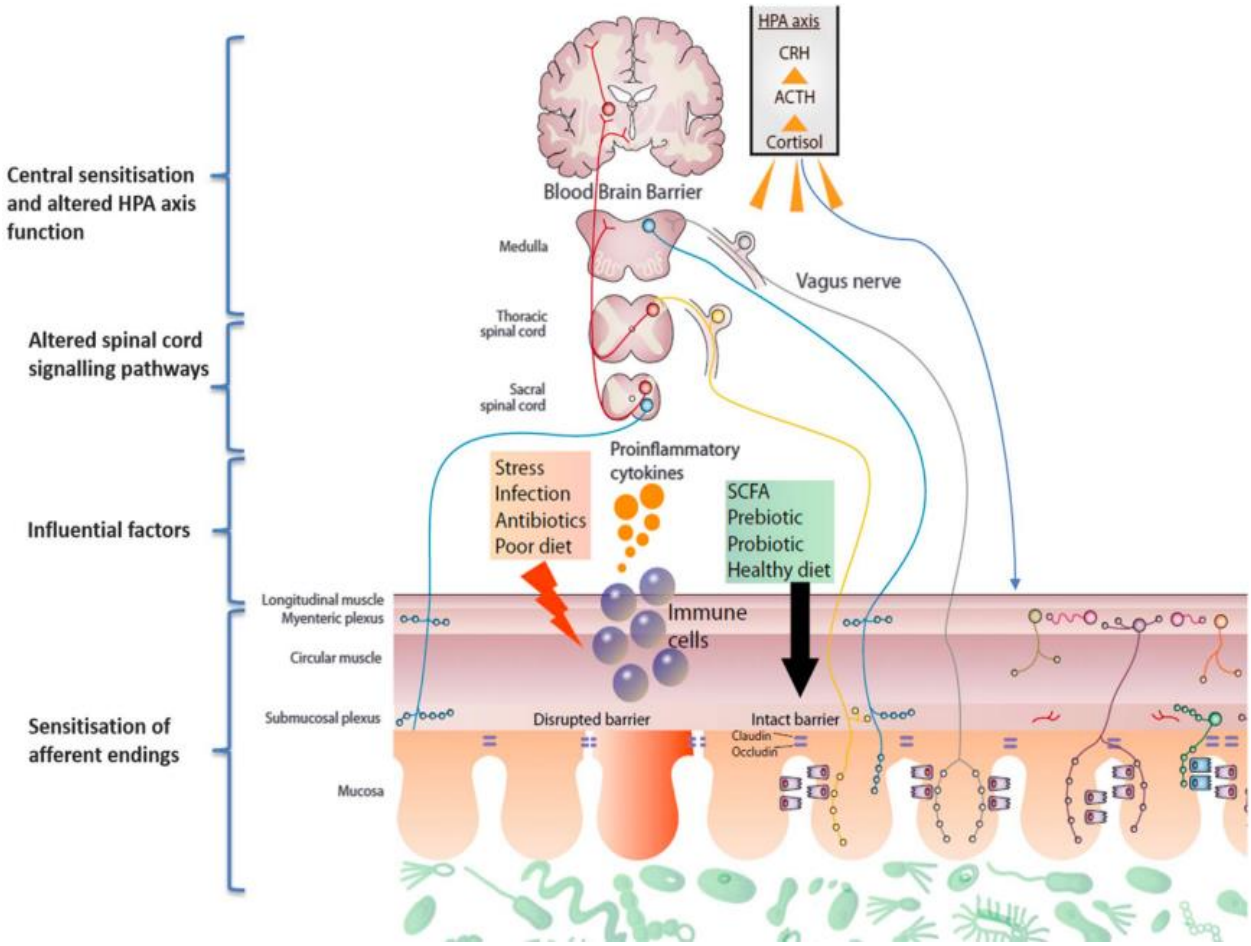


Figure 6: *Diagram and accompanying text reproduced from "The gut mocribiota as a key regulator of visceral pain" O'Mahony, S.M et al PAIN 2017 Apr (with permission).

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 5HT3 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 μ-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 μ-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 experiences 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 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' 16th 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.

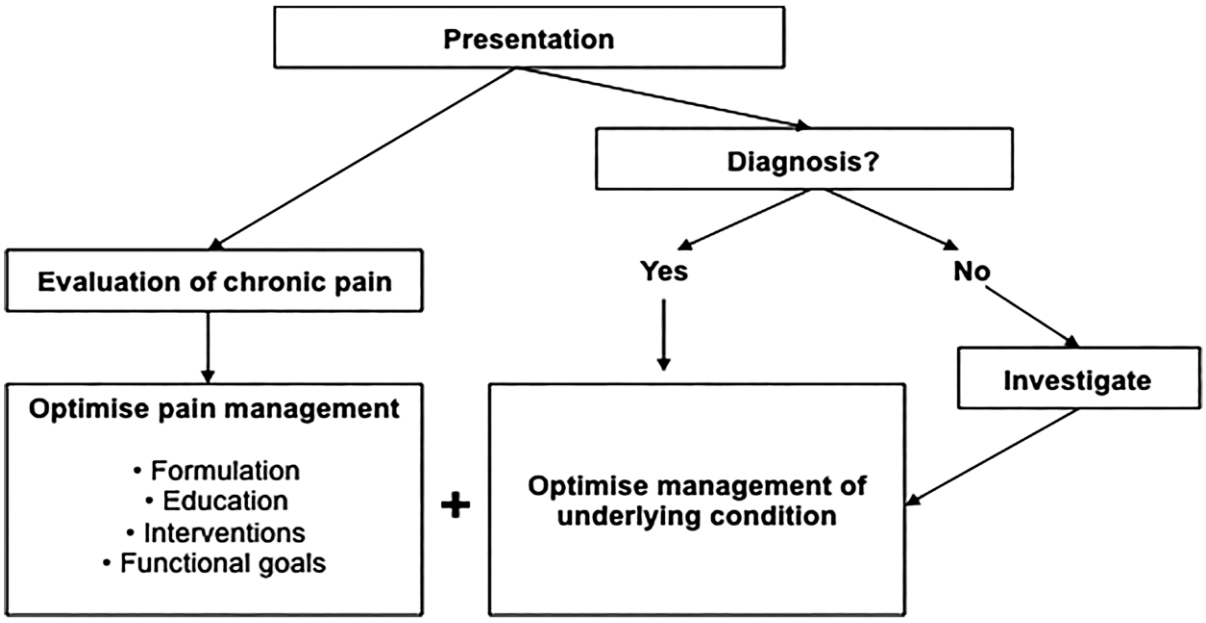


Figure 1: The clinical management of chronic pain at presentation

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 questionaires, 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.

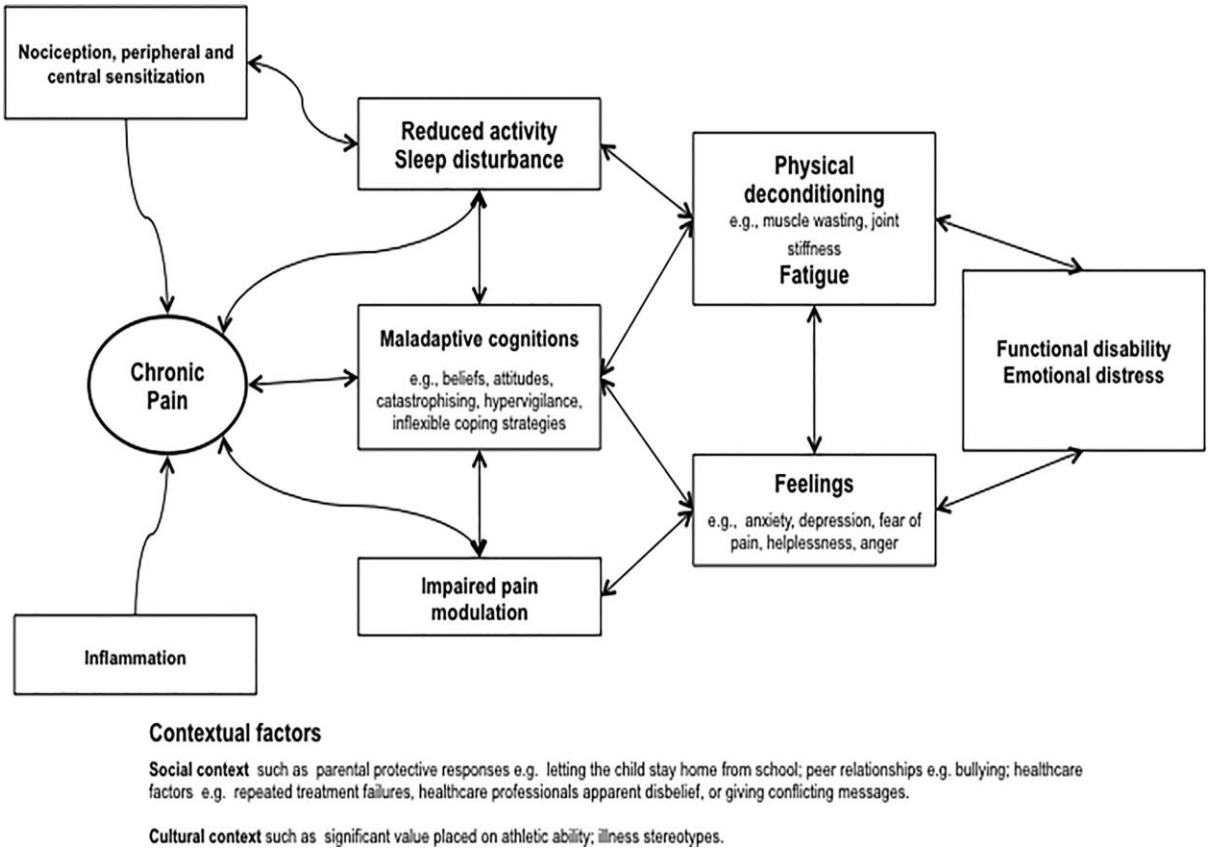


Figure 2: Generic formulation diagram for chronic inflammatory pain. reproduced with permission from Professor Christina Liossi (professor of health psychology, University of Southampton)

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)	• As required in combination or singly in all types of pain conditions but the effect for individuals is variable. • Long term use in inflammatory pain conditions but needs monitoring for side effects and efficacy.
Opioids	• Rarely indicated or effective in chronic non-cancer pain (except in some palliative care settings). • Side effects limit their efficacy and in the long term, tolerance, dependence and opioid induced hyperalgesia may cause further problems. • Other effects such as sleep associated breathing difficulties, pathological fractures, immunosuppression, cardiac and gastroenterological issues have been described.
Amitryptiline	• Effective in adults with neuropathic pain. • Effective in children with neuropathic pain and sleep disturbance. • May be effective in some patients with other pain conditions where central sensitisation is thought to be present, e.g., fibromyalgia
Gabapentin and pregabalin (Calcium channel blocking anticonvulsants)	• Effective for neuropathic pain in adults and children. • Pregabalin is effective for post-chemotherapy neuropathic pain.

- **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

Physical: Pain due to disease location Other symptoms e.g. nausea, constipation Physical decline & Fatigue	**Psychological** Grief, Depression Anxiety, Anger Adjustment to condition
Social Relationships with family and friends Role within the family School life	**Spiritual** Existential issues Meaning of life and illness Personal value as a human being Religious faith

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 spiritually 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 infront 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 psychologicalsymptoms

In the absence of a prompt psychiatric specialist review there are still several management options. This hold 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:
    - Relaxation therapy
    - 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[1].

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., hydraencephaly) 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) or Sleep Charity Children's Sleep Diary (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

Breethe: 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.

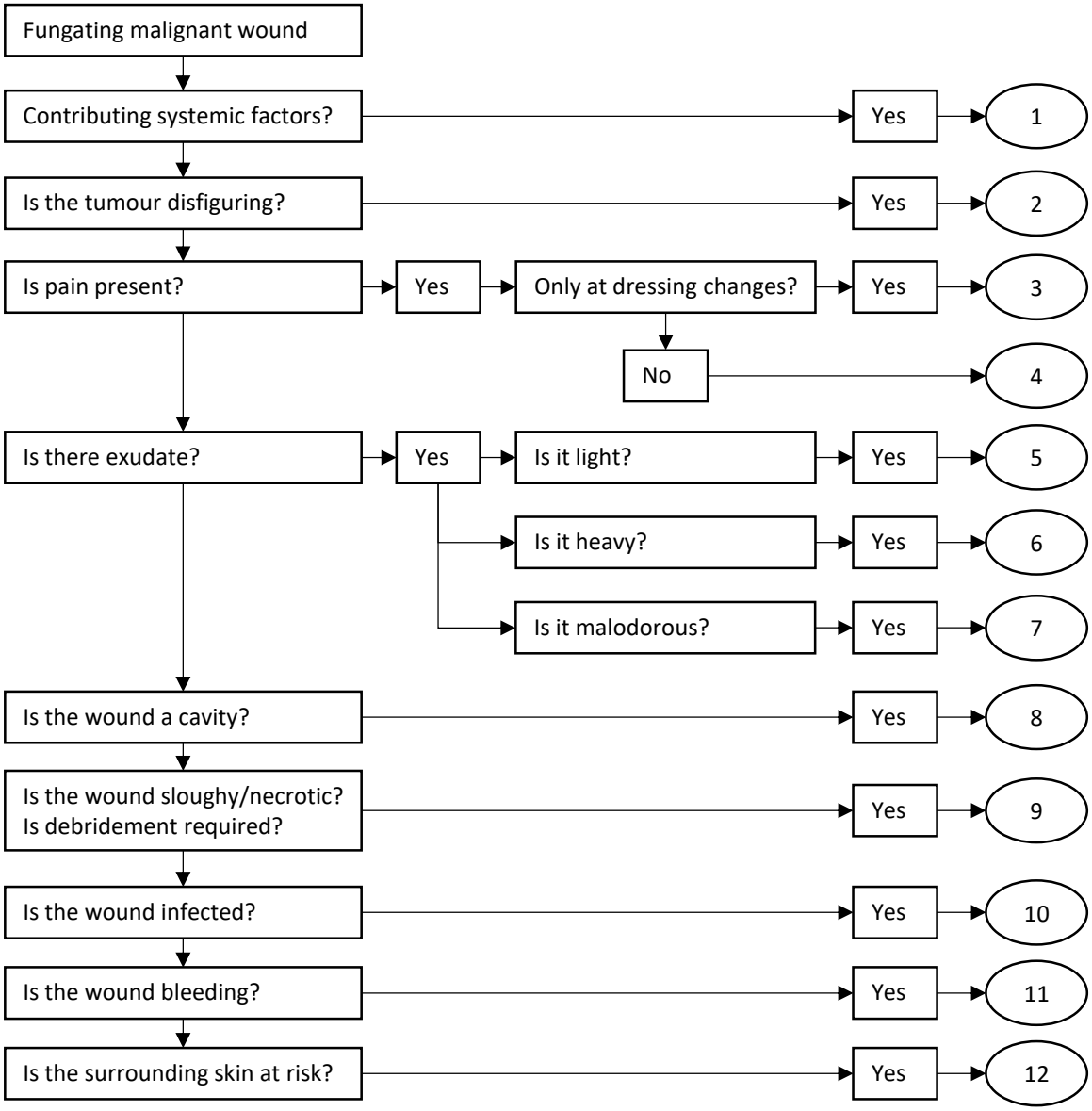
- Initial problems tend to start from pressure sores or friction burns.
- The skin at this stage can be protected with OpSite, Tegaderm or Cutifilm.
- Care must be taken when removing these dressings so as not to further damage the skin.
- Once it breaks down then DuoDerm or Spyrosorb can be used.
- 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	Lyofoam, Silastic.	Highly absorbent, good for deep cavities.	Not for wounds with sinuses.
Low adherent	Release Mepore.	Protects wound surface, absorb some exudates.	If dried out then wet to remove.

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

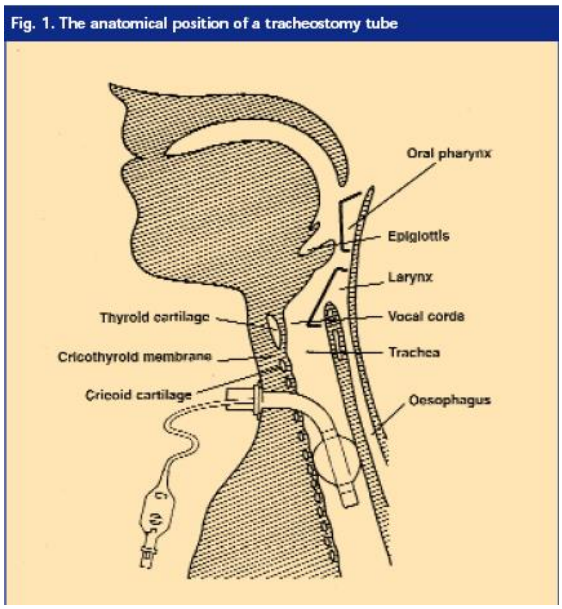
This is an artificial opening into the windpipe (trachea) which is held open by a tracheostomy tube. This helps the child to breathe easily; air now goes in and out through the tracheostomy, bypassing the mouth.

Indications for a tracheostomy

A narrow upper airway.

The need for long term ventilation.

Bronchial toilet.



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

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

- Suction machine and charger.
- Appropriate size suction catheters.

- Change of tracheostomy tube – same size and one size down.
- Change of ties/tapes.
- Scissors.
- Water based lubricant.
- Normal saline and gauze.
- Water to clear tubing.
- Gloves.
- Change of Swedish nose.
- Most importantly, a capable adult to change a tracheostomy in the event of an emergency.

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

Daily care

The tracheostomy stoma needs cleaning daily as tracheal secretions can infect the stoma site. Cleaning may need to be increased if 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 maintained at all times.

Suctioning

Why suction?

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

When to suction?

- Noisy breathing (sound of air bubbling through secretions).

- Visible secretions.
- A cough that sounds like secretions are in the tube.
- Restlessness/crying.
- Increased respiratory rate.

Suctioning instructions

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

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

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

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

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

- Tinged with blood?

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

Changing tracheostomy tube

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

Prepare equipment

- Round ended scissors.
- Two lengths of ¼ inch cotton tapes or Velcro tapes.
- New tube, check correct size and that the tube is intact.
- A smaller sized tube in case the correct size does not go in.
- Water based lubricant.
- Prepare tube, insert introducer, apply a small amount of lubricant on the outer tubing away from end of tube, place tube ready to use.

1. Position child as for tape change, older child can sit up.
2. Hold the tube (one person).
3. Second person cut and remove the dirty tapes and place clean tapes behind child's head.
4. First person holds tube; second person holds the new tube by flanges and positions the tip near the child's neck.
5. Gently remove the old tube following the curve of the tube. Same person firmly and gently slide in the new tube following the curve of the tube so as not to damage the trachea. Remove introducer if used.
6. Hold new tube securely.
7. If child is coughing allow to settle.

8. Check air flow through tube, child's breathing pattern and colour, suction if necessary.

9. Clean the skin around the tube. Tie the tapes.

10. Do not let go of the tube until the tapes are securely tied.

Humidification

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

Nebulising with a tracheostomy?

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

How to recognise blocked tube

- 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.
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
4th Floor, Fry Building
2 Marsham Street
London
SW1P 4DF

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

Formulary

Abbreviations

SRE= strong research evidence

WRE= some weak research evidence

NoRE= no published evidence but has clinical consensus

ARE= evidence (research or clinical consensus) with adults

SC = subcutaneous

IV = intravenous

IM= intramuscular

CSCI = continuous subcutaneous infusion

CorGA = corrected gestational age

In general (and when available), this Formulary includes, for palliative care, the same doses as those recommended in one or more of: British National Formulary (BNF)[337], British National Formulary for Children (BNFC)[338], Neonatal Formulary[339], WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses[235], Palliative Care Formulary[340]and Medicines for Children[341]. Readers outside the UK are advised to consult any local prescribing guidelines in addition to this Formulary.

The authors have made every effort to check current data sheets and literature up to September 2019, but the dosages, indications, contraindications and adverse effects of drugs change over time as new information is obtained. It is the responsibility of the prescriber to check this information with the manufacturer's current data sheet and we strongly urge the reader to do this before administering any of the drugs in this document. In addition, palliative care uses a number of drugs for indications or by routes that are not licensed by the manufacturer. In the UK such unlicensed use is allowed, but at the discretion and with the responsibility of the prescriber.

Acetazolamide

Use:

- Epilepsy
- Raised Intracranial Pressure – to reduce CSF production in obstructive causes, as an alternative to steroids
- Potential GABAA mediated analgesia at the spinal level

Dose and route:

Epilepsy

By mouth or slow intravenous injection:

- **Neonates:** Initially 2.5 mg/kg 2-3 times daily, followed by 5-7 mg/kg 2-3 times daily (maintenance dose)
- **Child 1 month–11 years:** initially 2.5 mg/kg 2-3 times daily, followed by 5-7 mg/kg 2-3 times daily, max 750 mg daily (maintenance dose)
- **Child 12-18 years:** 250 mg 2-4 times daily max 1 g per day

Raised Intracranial Pressure

By mouth or slow intravenous injection: 8mg/kg three times a day, increased as necessary to max 100mg/kg/day.

Notes:

- Carbonic anhydrase inhibitor. Licensed for raised intracranial pressure and epilepsy in childhood. Also used outside of licence for glaucoma.
- Acetazolamide may give symptomatic benefit in the case of CSF obstruction.
- This may translate to benefit in cases of inoperable brain tumours, causing obstruction to drainage of CSF, rather than just mass effect (where pulses of steroid may be more appropriate).
- There have also been suggestions of GABAA receptor mediated analgesia at the spinal level, as a consequence of carbonic anhydrase inhibition.
- Do NOT use IM / SC as very painful due to alkaline pH.
- May cause electrolyte disturbance with prolonged use (can be corrected with potassium bicarbonate). GI disturbances and paraesthesia reported at higher doses.
- Note contraindications include sulphonamide sensitivity, adrenocortical insufficiency, hypokalaemia, hyponatraemia. (Monitor blood count and electrolytes in prolonged use).
- Has considerable drug interactions with other medications.
- Peak plasma concentration 1-2 hours after administration of tablet.
- Available as 250 mg tablets; modified release capsules 250 mg; 500 mg injection (sodium salt, powder for reconstitution) Diamox®.
- Can be used via feeding tubes without causing blockage: tablets are scored and can be halved or quartered. Dissolving tablet in 10ml water produces a coarse dispersion that settles rapidly. Syringe and container should therefore be well rinsed and the residue administered to ensure the full dose is given. No specific data for jejunal administration: monitor for increased side effects or lack of efficacy. Injection can theoretically be used via feeding tubes, but costly. NB modified release capsules unsuitable for feeding tube administration.

Evidence: [337, 338, 340, 342-346] NoRE

Adrenaline *(topical) (also known as Epinephrine)*

Use:

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

Dose and routes:

For bleeding: Soak gauze in 1:1000 (1mg/mL) solution and apply directly to bleeding point for up to 10 minutes. (Short term use only due to risk of ischaemic necrosis and rebound vasodilatation).

For upper airway obstruction: By inhalation of nebulised solution

1 month-11 years: 400 micrograms/kg (max: 5 mg per dose).
Can repeat in 30 mins. Clinical effect 2-3 hours. 1:1000 (1 mg/mL) solution diluted with 0.9% saline nebulised.

Evidence: [337-340] NoRE

Alfentanil

Use:

- Short acting synthetic lipophilic opioid analgesic derivative of fentanyl.
- Used as analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia).
- Alternative opioid if intolerant to other strong opioids; useful in renal failure if neurotoxic on morphine, or stage 4 to 5 severe renal failure.
- Useful for breakthrough pain and procedure-related pain.

Dose and Routes:

1. ***Analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia).*** **SEEK SPECIALIST ADVICE**

By IV/SC bolus *(**these doses assume** assisted ventilation is available)*

- **Neonate:** 5-20 micrograms/kg initial dose, (slow bolus over 30 seconds) up to 10micrograms/kgsupplemental doses
- **1 month-17 years:** 10-20 micrograms/kg initial dose, (slow bolus over 30 seconds). Up to 10micrograms/kg supplemental doses

By continuous IV or SC infusion (***these doses assume** assisted ventilation is available*)

- **Neonate:** 10-50 micrograms/kg over 10 minutes then 30-60micrograms /kg/ hour
- **1 month-17 years**: 50-100 microgram/kg loading dose over 10 minutes, then30-60microgram/kg/hour as a continuous infusion

2. ***Alternative opioid if intolerant to other strong opioids; useful in renal failure if neurotoxic on morphine, or stage 4 to 5 severe renal failure.***
   SEEK SPECIALIST ADVICE.

Doses should be based on opioid equivalence with the following suggested as safe and practical conversion ratios.
Oral morphine to CSCI alfentanil: 1/30 of the 24-hour total oral morphine dose
e.g. oral morphine 60 mg/24 hours = alfentanil 2 mg/24 hours CSCI.

CSCI/IV morphine to CSCI alfentanil: 1/15 of the 24-hour total CSCI/IV morphine dose
e.g. morphine 30 mg/24 hours CSCI/IV = alfentanil 2mg/24 hours CSCI.

CSCI diamorphine to CSCI alfentanil: 1/10 of the 24-hour total diamorphine dose
e.g. diamorphine 30 mg/24 hours = alfentanil 3 mg/24 hours CSCI.

If conversion is due to toxicity of the previous opioid, lower doses of alfentanil may be sufficient to provide adequate analgesia.

Opioid naïve Adults: CSCI 500 microgram-1 mg over 24 hours.

3. ***Breakthrough pain*** **SEEK SPECIALIST ADVICE**

SC / Sublingual / Buccal

Suggest 10-16% of the total CSCI dose. However there is a very poor relationship between the effective PRN dose and the regular background dose, so start with low dose and titrate. Alfentanil has a quick onset of action (within 5 minutes after subcutaneous bolus injection), but short duration of action (under 60 minutes). Even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Dose and frequency of administration should be regularly reviewed.

4. ***Procedure-related pain*** **SEEK SPECIALIST ADVICE**

SC / Sublingual / Buccal

- **Adults** (assuming spontaneous unsupported respiration): 250-500 microgram single dose over 30 seconds. Subsequent doses 250microgram. Doses differ if assisted ventilation.
- **Child:** 5 microgram/kg single dose.

Give dose at least 5 minutes before an event likely to cause pain; repeat if needed.

Notes:

- Licensing: Alfentanil injection is licensed for use in children as an analgesic supplement for use before and during anaesthesia. Use for pain relief in palliative care is unlicensed. Buccal, sublingual or intranasal administration of alfentanil for incident/breakthrough pain is an unlicensed indication and route of administration.
- Useful for incident and breakthrough pain as faster onset, shorter acting, smaller volumes required compared with fentanyl. Dose required for breakthrough pain does not correlate with background analgesia requirement.
- There is limited information / evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.
- Potency: 10-20 times stronger than parenteral morphine, approximately 25% of the potency of fentanyl.
- Very useful in patients with severe renal failure (no dose reduction is needed). May need to reduce the dose 30-50% in severe hepatic impairment.
- To avoid excessive dosage in obese children, the dose may need to be calculated on the basis of ideal weight for height, rather than actual weight.
- Pharmacokinetics: half-life is prolonged in neonates, so can accumulate in prolonged use. Clearance may be increased in patients from 1 month to 12 years of age, so higher infusion doses may be needed.
- Contraindication: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Interaction: alfentanil levels are increased by inhibitors of Cytochrome P450.
- Adverse effects include respiratory depression, hypotension, hypothermia, muscle rigidity (which can be managed with neuromuscular blocking drugs).
- Metabolised by CYP3A4 and CYP3A5, so note potential interactions (including midazolam).
- For SC or IV infusion, alfentanil is compatible with 0.9% NaCl or 5% glucose as a diluent. For CSCI alfentanil appears physically compatible with most drugs used in a syringe driver. There

is evidence for compatibility with midazolam. Note possible concentration-dependent incompatability with cyclizine: use water for injection as diluent and observe for crystallisation. Like diamorphine, high doses of alfentanil may be dissolved in small volumes of diluent which is very useful for SC administration.

- Available as: injection (500 microgram/mL in 2 ml and 10 ml ampoule); Intensive care injection (5 mg/mL in 1ml ampoule which must be diluted before use). Nasal spray with attachment for buccal / SL use (5 mg/5 mL bottle available as special order from Torbay Hospital Manufacturing Unit Tel: 01803 664707. Each 'spray' delivers 0.14 ml = 140 microgram alfentanil. More costly than using injection preparation).
- Schedule 2 CD

Evidence: [337, 338, 340, 341, 347-350]
ARE, SRE (for PICU settings), NoRE (in palliative care settings outside ICU)

Amitriptyline

Use:

- Neuropathic pain
- Drooling, refractory cough (same dosing)

Dose and routes:
By mouth:

- **Child 2–11 years:** Initial dose of 200 microgram/kg (maximum 10mg) given once daily at night. Dose may be increased gradually, if necessary and beneficial, to a suggested maximum of 1mg/kg/dose twice daily (under specialist supervision).
- **Child 12–17 years:** Initial dose of 10mg at night increased gradually, if necessary, every 3-5 days to a suggested initial maximum of 75 mg/day.
  Higher doses up to 150 mg/day in divided doses may be used under specialist advice.

(Twice daily dosing rarely needed, if used then give 25-30% of daily dose in morning and 30-75% at night).

Notes:

- Not licensed for use in children with neuropathic pain, drooling or cough.
- Analgesic effect unlikely to be evident for several days. Potential improved sleep and appetite which are likely to precede analgesic effect.
- Patient information; see Medicines for Children leaflet: 'Amitriptyline for neuropathic pain'. https://www.medicinesforchildren.org.uk/amitriptyline-neuropathic-pain-0
- For intractable cough, benefit probably relates to reducing cough reflex hypersensitivity.
- Drug interactions: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation. Caution with concurrent use of drugs which inhibit or induce CYP2D6 enzymes. Concurrent carbamazepine use reduces plasma amitriptyline by up to 60%.
- Contraindicated in severe liver impairment and arrhythmias.
- Main side effects limiting use in children include: constipation, dry mouth, blurred vision and drowsiness.
- Absorbed slowly from gastrointestinal tract. Peak plasma concentration occurs 4-8 hours after oral administration. Liquid 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 tablets via enteral feeding tube: they can be crushed to disperse in water for immediate administration but don't easily disperse.
- No specific data available for jejunal administration: monitor for increased side effects or loss of efficacy.
- Available as: tablets (10 mg, 25 mg, 50 mg) and oral solution (10 mg/5 mL,

25 mg/5 mL, 50 mg/5 mL; other strengths may be available as 'specials').

Evidence: [337, 338, 340, 345, 351-355]

Aprepitant

Use:

- Prevention and treatment of nausea and vomiting associated with moderate or highly emetogenic cancer chemotherapy.

Dose and route:
For oral administration:

- **Child 6 months–11 years:** 3 mg/kg (max 125 mg) as a single dose on Day 1(1 hour before chemotherapy) followed by 2 mg/kg (max 80 mg) as a single dose on Day 2 and Day 3
- **Child >12 years:** 125 mg as a single dose on Day 1 (1 hour before chemotherapy) followed by 80 mg as a single dose on Day 2 and Day 3

Aprepitant is used in combination with a corticosteroid (usually dexamethasone) and a 5-HT3 antagonist such as ondansetron.

Notes:

- Aprepitant is licensed for the prevention of acute and delayed nausea and vomiting associated with highly or moderately emetogenic cancer chemotherapy in adults, children and infants from 6 months of age (>6kg). Role in palliative care unclear.
- Aprepitant also has a role in treating pruritus, particularly due to chemotherapy or mixed causes.
- Aprepitant is a selective high-affinity antagonist at neurokinin NK_1 receptors (in Vomiting Centre and Chemoreceptor Trigger Zone).
- Aprepitant is a substrate, a moderate inhibitor and inducer of the CYP3A4 isoenzyme system. It is also an inducer of CYP2C9 and therefore has the potential to interact with any other drugs that are also metabolised by these enzyme systems including rifampicin, carbamazepine, phenobarbital, itraconazole, clarithromycin, warfarin and dexamethasone. Please note this list is not exhaustive – seek advice.
- Common side effects include hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache and dizziness.
- Available as: capsules 80 mg and 125 mg. Powder for an oral suspension (25 mg/ml) has recently been approved by the European Medicines Agency, but there is not currently a UK launch date. In the interim, a formulation is available for extemporaneous preparation of an oral suspension.

Evidence: [337, 340, 356-361]

Arachis Oil Enema

Use:

- Faecal softener
- Faecal impaction

Dose and route:
By rectal administration

- **Child 3-6 years:** 45-65 mL as required (~1/3 to 1/2 enema)
- **Child 7-11 years:** 65 mL - 100 mL as required (~1/2 to 3/4 enema)
- **Child 12 years and over:** 100-130 mL as required (~3/4 to1 enema).

Notes:

- **Caution: as arachis oil is derived from peanuts, do not use in children with a known allergy to peanuts.**
- Generally used as a retention enema to soften 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.
- Warm enema before use by placing in warm water.
- Administration may cause local irritation.
- Licensed for use in children.
- Available as: enema, arachis (peanut) oil in 130mL single dose disposable packs.

Evidence: [337, 338, 340, 341] NoRE

Atropine

Use:

- Reductionof death rattle
- Hypersalivation / Hypersecretion

Dose and route:
By sublingual administration

- **Neonates:** Injection solution, 20-40 micrograms/kg/dose 2-3 times a day as required,
- **Child 10-19kg:** Eye drop solution 0.5%, 1 drop three times a day at 6 hourly intervals.
- **Child 5-18 years (>20 kg):** Eye drop solution 0.5-1%,1-2 drops 4-6hourly intervals

Notes:

- Not licensed for these conditions.
- Research evidence based on 0.5% eye drops, not avaliable in UK but available in other parts of world.
- Use only where symptom is affecting quality of life. Used 3rd line if glycopyrronium or hyoscine are not avaliable or effective.
- Concurrent treatment with 2 or more antimuscarinic drugs increases risk of side effects and central toxicity. Children are particularly susceptible.
- In palliative care patients, the number of antimuscarinic drugs used is associated with worsening quality of life.
- Monitor for anticholinergic side effects.
- Sublingual administration: use eye drops unless neonate (in which case use injection solution sublingually).
- Available as 1% (10 mg/ml) eye drops. 10 ml or 0.5 ml pack size.). 0.5% eye drops in other parts of world. Injection 400 micrograms/mL, 600 micrograms /mL, 1 mg/mL ampoules.

Evidence: [337, 362-369] WRE

Baclofen

Use:

- Chronic severe spasticity or spasms of voluntary muscle
- Considered as third line neuropathic agent
- Hiccup (strong evidence in adults but none in children)

Dose and routes:
By mouth:

- **Initial dose for child under 18 years:** 300 microgram/kg/day in 4 divided doses, increased gradually at weekly intervals to a usual maintenance dose of 0.75-2 mg/kg/day in divided doses with the following maximum daily doses:
- **Child 1 month-7 years:** maximum total daily dose 40 mg/day
- **Child 8-18 years:** maximum total daily dose 60 mg/day

By Intrathecal injection:

- By specialist teams only. Maintenance 25-200micrograms daily via intrathecal pump.

Notes:

- Review treatment for spasticity if no benefit within 6 weeks of achieving maximum dose, and withdraw over 1-2 weeks if ineffective.
- Patient information: See Medicines for Children leaflet 'Baclofen for muscle spasm': www.medicinesforchildren.org.uk/baclofen-muscle-spasm
- Dependence and tolerance are unlikely, so preferable to diazepam.
- Likely onset of action for hiccups 4-8 hours, for muscle spasm in 1-2 days, for spasticity 3-4 days.
- For severe intractablehiccups –lower dose range to be used. May have direct effect on diaphragm.
- Balance efficacy against unwarranted additional effects of baclofen.
- There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.
- Administer after food to reduce risk of gastric irritation.
- Monitor and review reduction in muscle tone and potential adverse effects on swallow, airway protection, posture and function. Drowsiness and nausea are common side effects.
- Impact of undesirable hypotonia may be minimised by reducing daytime and increasing evening doses.
- Intrathecal use may be considered, by specialist only, for severe chronic spasticity, if enteral treatment does not achieve control, is poorly tolerated, or higher doses are required.
- Avoid abrupt withdrawal as can precipitate serious psychiatric reactions and (especially after intrathecal use), life-threatening withdrawal syndrome including hyperactivity, increased spasticity, autonomic dysfunction. See PCF6 for management of this.
- Baclofen CSCI (using intrathecal preparation) may be used short term (after a test dose) to avoid sudden withdrawal when enteral and/or intrathecal routes become impossible.
- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.
- Contraindicated if there is a history of active peptic ulceration.
- Administration with or after food may minimise gastrointestinal irritation side effects.

- Peak plasma concentration achieved 0.5-1.5 hours after oral dose (site of absorption not documented).
- 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).
- Available as: tablets (10 mg) and oral solution (5 mg/5 mL). Also intrathecal solution for infusion, for specialist 500 microgram/ml and 2 mg/ml.

Evidence: [193, 337, 338, 340, 345, 370-378]

Bethanechol

Use:

- Opioid induced urinary retention

Dose and routes:
By mouth:

- **Child over 1 year:** 0.6 mg/kg/day in 3 or 4 divided doses. Maximum single dose 10mg.
- **Adult dose:** 10-25 mg per dose 3 to 4 times a day. Occasionally it may be felt necessary to initiate therapy with a 50 mg dose.

Subcutaneous:

- **Child over 1 year:** 0.12 to 2 mg/kg/day in 3 or 4 divided doses. Maximum single dose 2.5mg,
- **Adult dose:** 2.5 to 5 mg per dose 3 to 4 times a day.

Notes

- The safety and efficacy of bethanechol in children has not been established (bethanechol is not licensed for use in children).
- Preferably taken 1 hour before or 2 hours after food to reduce potential for nausea and vomiting.
- Contraindicated in hyperthyroidism, peptic ulcer, asthma, cardiac disease and epilepsy.
- Tablets may be crushed and dispersed in water for immediate administration via an enteral feeding tube; formulation for extemporaneous oral suspension is available.
- No specific data for jejunal administration: monitor for increased side effects or loss of efficacy.
- Poorly absorbed by gastrointestinal tract. Therapeutic effect seen within 1 hour of oral administration.
- Available as: 10 mg and 25 mg tablets licensed in UK, other strengths via importation companies and NOT licensed in UK.

Evidence: [9, 337, 345]

Bisacodyl

Use:

- Constipation

Dose and routes:
By mouth:

- **Child 4–17 years:** 5-20 mg once daily (recommended to be taken at night) adjust according to response.

By rectum (suppository):

- **Child 2–17 years:** 5-10 mg once daily; adjust according to response.

Notes:

- Tablets act in 10–12 hours. Suppositories act in 20–60 min; suppositories must be in direct contact with mucosal wall.
- Tablets should not be crushed.
- Stimulant laxative. Acts by topical effect on the colonic mucosa.
- Prolonged or excessive use can cause electrolyte disturbance.
- Tablets not suitable for enteral tube administration.
- Available as: gastro-resistant tablets (5 mg) and suppositories (5 mg, 10 mg).

Evidence: [337, 338, 379]

Buprenorphine

Use:

- Moderate to severe pain

Dose and routes:
By sublingual route (starting doses; we recommend starting at the lower recommended dose of the range):

- **Child body weight 16–25 kg:** 100 micrograms every 6–8 hours
- **Child body weight 25–37.5 kg:** 100–200 micrograms every 6–8 hours
- **Child body weight 37.5–50 kg:** 200–300 micrograms every 6–8 hours
- **Child body weight over 50 kg:** 200–400 micrograms every 6–8 hours

By CSCI

- **Adult/ older adolescents** starting dose of 300 micrograms/24 hours, dilute with WFI NaCl or 5% glucose
- Stable with glycopyrronium and haloperidol

By transdermal patch:

- By titration or as indicated by existing opioid needs.

Buprenorphine patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 12 mg daily	≡ *BuTrans®* '5' patch	7-day patches
morphine salt 24 mg daily	≡ *BuTrans®* '10' patch	7-day patches
morphine salt 48 mg daily	≡ *BuTrans®* '20' patch	7-day patches
morphine salt 84 mg daily	≡ *Transtec®* '35' patch	4-day patches
morphine salt 126 mg daily	≡ *Transtec®* '52.5' patch	4-day patches
morphine salt 168 mg daily	≡ *Transtec®* '70' patch	4-day patches

NB There are higher strength SL tablets also available but these are indicated as an adjunct in the treatment of opioid dependence. Take care with prescribing.

Notes:

- Sublingual tablets not licensed for use in children < 6 years old.
- Patches not licensed for use in children.
- Patches may cause contact allergies. Pre-treatment topically with budenoside inhalation spray to the area the patch is applied to may help.
- Causes less constipation than some other opioids.
- Athough no actual published evidence, in theory has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Not fully reversible with naloxone at least not with the regular dose since the binding capacity is so high you have to use much higher doses than regularly used.
- Sublingual duration of action 6-8 hours.
- Caution with hepatic impairment and potential interaction with many drugs including anti-retrovirals.

- Available as: tablets (200 microgram, 400 microgram) for sublingual administration. Tablets may be halved.

  Available as: several brands (and generics) of transdermal patches with 72-hour, 96 hour and 7 day release profiles. Only matrix patches can be cut.

1. BuTrans®, Butec®, Bupramyl®, Panitaz®, Reletrans®, Sevodyne®—applied every 7 days. Available as 5 (5 micrograms /hour for 7 days), 10 (10 micrograms /hour for 7 days), 15 (15 micrograms/hour for 7 days) and 20 (20 micrograms /hour for 7 days).
2. Bupeaze®, Buplast®, Relevtec®, TransTec®, —applied every 96 hours. Available as 32.5 (32.5 micrograms /hour for 96hours), 52.5 (52.5 micrograms /hour for 96hours), and 70 (70 micrograms /hour for 96hours).
3. Hapactasin® – applied every 72 hours. Available as 35 (35 micrograms/hour for 72 hours), 52.5 (52.5 micrograms/hour for 72 hours) and 70 (70 micrograms/hour for 72 hours)
4. IV/SC solution 300 micrograms/ml

For patches, systemic analgesic concentrations are generally reached within 12–24 hours 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 - give regular morphine doses for the first 12 hours after applying the patch.
- 12-hourly slow-release morphine - apply the patch and give the final slow-release dose at the same time.
- 24-hourly slow-release morphine - apply the patch 12 hours after the final slow-release dose.
- Continuous subcutaneous infusion - continue the syringe driver for about 12hours after applying the patch.

- Rate of absorption from patch isaffected by temperature, so caution with pyrexia or increased external temperature such as hot baths: possibility of accidental overdose with respiratory depression.
- Patches are finding a use as an easily administered option for low dose background opioid analgesia in a stable situation, for example in severe neurological impairment.
- Schedule 3 CD (CD No Register).

Evidence: [280, 337, 338, 340, 380-393]

Carbamazepine

Use:

- Neuropathic pain

- Some movement disorders
- Anticonvulsant

Dose and routes
By mouth:

- **Neonates:** Experience is limited. Initial dose 5 mg/kg twice daily.
- **Child 1 month–11 years:** Initial dose of 5 mg/kg at night or 2.5 mg/kg twice daily, increased as necessary by 2.5-5 mg/kg every 3–7 days; usual maintenance dose 5 mg/kg 2–3 times daily. Doses up to 20 mg/kg/day in divided doses have been used.
- **Child 12–17 years:** Initial dose of 100–200 mg 1–2 times daily; increased slowly to usual maintenance of 200-400 mg 2–3 times daily. Maximum 1.8 g/day in divided doses.

By rectum:

- **Child 1 month–17 years:** Use approximately 25% more than the oral dose (maximum single dose 250 mg) up to 4 times a day.

Notes:

- Not licensed for use in children with neuropathic pain.
- Can cause serious blood, hepatic, and skin disorders. Parents should be taught how to recognise signs of these conditions, particularly leucopoenia.
- Numerous interactions with other drugs including chemotherapy drugs.
- May cause hyperalgesia on abrupt withdrawl.
- Patients taking carbamazepine alone or in combination with phenytoin appear to need more fentanyl than those not taking these antiepileptics. Carbamazepine appears to increase the production of a more potent metabolite of codeine, normorphine. Carbamazepine reduces tramadol concentrations, appears to reduce oxycodone concentrations and is predicted to reduce the concentration and efficacy of buprenorphine.
- Different preparations may vary in bioavailability so avoid changing formulations or brands.
- Suppositories of 125 mg are approximately equivalent to 100 mg tablets.
- Oral liquid has been administered rectally – should be retained for at least 2 hours if possible but may have a laxative effect.
- For administration via an enteral feeding tube use the liquid preparation. Dilute with an equal volume of water immediately prior to administration. Due to high viscosity it needs to be pushed through with a syringe. If giving doses higher than 400 mg/day, divide into 4 equal doses. Doses above 800 mg/day may cause bloating due to the sorbitol content of the liquid. There is no specific data relating to jejunal administration of carbamazepine. Administer using the above method. An increase in side-effects such as dizziness is possible owing to the rapid delivery into the small bowel. Monitor for increased side-effects or loss of efficacy. Consider decreasing the dose and increasing the dosing frequency if side-effects are problematic.
- Available as: tablets (100 mg, 200 mg, 400 mg), liquid (100 mg/5 mL), suppositories (125 mg, 250 mg), and modified release tablets (200 mg, 400 mg).

Evidence: [338, 345, 394-399]

Celecoxib

Use:

- Pain, inflammatory pain, bone pain, stiffness. Not used first line.
- Dose based on management of juvenile rheumatoid arthritis.

Dose and routes
By mouth:

- **Child over 2 years:**
  - Weight 10-25 kg: 2-3 mg/kg/dose twice a day
    (Maximum 50 mg twice daily or 100 mg daily)
  - Weight more than 25 kg: 100 mg twice daily
- **Over 16 years**: Adult dose of 100 mg BD. Can be doubled in severe pain to 200 mg BD

Notes

- Celecoxib is a cyclo-oxygenase-2 selective inhibitor.
- Not licensed in the UK for use in children.
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factorsor duration of NSAID use. However, the greatest risk may be in those receiving high doses long term. COX-2 inhibitors are also associated with an increased risk of thrombotic effects.
- All NSAIDs are associated with serious gastro-intestinal toxicity. COX-2 inhibitors are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs. May exacerbate Crohn's disease.
- No difference in tolerability or efficacy has been shown between etoricoxib, naproxen and celecoxib.
- Use with caution in patients with renal impairment and avoid in severe renal impairment.
- Use with caution in hepatic impairment.
- Celecoxib interacts with a great many commonly used drugs. Check BNF (current version on-line). Reduce dose by 50% if using fluconazole.
- Capsules may be opened and contents mixed with soft food immediately before administration. For administration via an enteral feeding tube, the capsule may be opened and the contents mixed with water to form a milky suspension. For a 50 mg dose, approximately halve the 100 mg capsule contents to give a best estimate of a 50 mg dose. However, as the capsules are small, this is difficult to do accurately.
- Available as: capsules 100 mg, 200 mg.
- For SC /IM use use parecoxib adolescents 40-80 mg/24 hr CSCI or 20 mg SC PRN. For CSCI give parecoxib alone and diluted to a volume of 22 ml in 0.9% NaCl to reduce the risk of site reaction.

Evidence: [337, 400-407] WRE

Chloral hydrate

Use:

- Insomnia
- Agitation
- Seizures in severe epileptic encephalopathy (seek specialist advice)
- Status Dystonicus (seek specialist advice)
- Neonates; Sedation for procedures

Dose and routes:
By mouth or rectum:

- **Neonate:** Initial dose of 30 mg/kg as a single dose at night. May be increased to 45mg/kg at night or when required.
- **Neonates- for sedation for procedures in NICU:** 30–50 mg/kg 45–60 minutes before procedure; doses up to 100 mg/kg may be used with respiratory monitoring.

- **Child 1 month–11 years:** Initial dose of 30 mg/kg as a single dose at night. May be increased to 50 mg/kg at night or when required.
  Maximum single dose 1 g.
- **Child 12–17 years:** Initial dose of 500 mg as a single dose at night or when required. Dose may be increased if necessary to 1-2 g. Maximum single dose 2 g.

Notes:

- Not licensed for agitation or in infants <2 years for insomnia.
- Prolonged half-life in neonates.
- Oral use: mix with plenty of juice, water, or milk to reduce gastric irritation and disguise the unpleasant taste. Light-sensitive so needsto 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 although there is little information and it is important to remember it can cause gastric irritation. Suggest the dose is diluted with water to minimise this. There is no specific data relating to the jejunal administration of chloral hydrate. Monitor for loss of efficacy or increased side-effects.
- Accumulates with prolonged use and should be avoided in severe renal or hepatic impairment.
- Available as: tablets (chloral betaine 707 mg = choral hydrate 414 mg— Welldorm®), oral solution (143.3 mg/5 mL—Welldorm®; 200 mg/5 mL, 500 mg/5 mL both of which are available from 'specials' manufacturers or specialist importing companies), suppositories (available as various strengths 25 mg, 50 mg, 60 mg, 100 mg, 200 mg, 500 mg from 'specials' manufacturers).

Evidence: [338, 339, 341, 408-418]

Chlorpromazine

Use:

- Hiccups
- Nausea and vomiting of terminal illness (where other drugs are unsuitable)
- Agitated delirium at the end of life

Dose and routes:

Hiccups
By mouth:

- **Child 1–5 years:** 500 micrograms/kg every 4–6 hours adjusted according to response (maximum 40 mg daily)
- **Child 6–11 years:** 10 mg 3 times daily, adjusted according to response (maximum 75mg daily)
- **Child 12–17 years:** 25 mg 3 times daily (*or* 75 mg at night), adjusted according to response, higher doses may be used by specialist units.

Nausea and vomiting of terminal illness (where other drugs are unsuitable)
By mouth:

- **Child 1–5 years:** 500 micrograms/kg every 4–6 hours; maximum 40 mg daily
- **Child 6–11 years**: 500 micrograms/kg every 4–6 hours; maximum 75 mg daily
- **Child 12–17 years:** 10–25 mg every 4–6 hours.

By deep intramuscular injection:

- **Child 1–5 years:** 500 micrograms/kg every 6–8 hours; maximum 40 mg daily
- **Child 6–11 years**: 500 micrograms/kg every 6–8 hours; maximum 75 mg daily
- **Child 12–17 years:** initially 25 mg then 25–50 mg every 3–4 hours until vomiting stops.

Notes:

- Not licensed in children for intractable hiccup.
- Caution in children with hepatic impairment (can precipitate coma), renal impairment (start with small dose; increased cerebral sensitivity), cardiovascular disease, epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis.
- Caution is also required in severe respiratory disease and in children with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops).
- Photosensitisation may occur with higher dosages; children should avoid direct sunlight.
- Antipsychotic drugs may be contra-indicated in CNS depression.
- Risk of contact sensitisation; tablets should not be crushed and solution should be handled with care.
- Oral solution may be administered via an enteral feeding tube. There is no specific data relating to the jejunal administration of chlorpromazine. Monitor for loss of efficacy or increased side-effects.
- Available as: tablets, coated (25 mg, 50 mg, 100 mg); oral solution (25 mg/5 mL,100 mg/5 ml ; injection (25 mg/mL in 50 mg/2 mL ampoules).
- Over 16 years may have 100 mg base rectally. For equivalent therapeutic effect 100 mg chlorpromazine base given *rectally* as a suppository ≡
- 20–25 mg chlorpromazine hydrochloride *by intramuscular injection* ≡

- 40–50 mg of chlorpromazine base or hydrochloride given *by mouth*.But rectal administration is unlicensed use.
- Suppositories from specials manufacturers.

Evidence: [207, 208, 337, 338, 419-426]

Clobazam

Uses:

- Adjunctive therapy for epilepsy
- Short term 'add on' therapy for epilepsy exacerbations related to hormonal changes or intercurrent illness

Dose and route:
For oral administration:

- **Child 1 month–5 years:** Initial dose of 125 micrograms/kg twice daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 250 micrograms/kg twice daily. Maximum dose 500 micrograms/kg (15 mg single dose) twice daily.
- **Child 6-17 years:** Initial dose of 5 mg daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 0.3-1 mg/kg daily. Maximum 60 mg daily. Daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided.

Notes:

- Not licensed for use in children less than 6 years of age.
- Once titrated to an effective dose of clobazam, patients should remain on their treatment (except when being used for short courses) and care should be exercised when changing between different formulations.
- Tolerance in longer term use may be managed by 'switching/rotating' benzodiazepines.
- Tablets can be administered whole or crushed and mixed in apple sauce. The 10mg tablets can be divided into equal halves of 5 mg. Clobazam can be given with or without food. Both oral liquid and normal tabletsdispersed in water may be administered via an enteral feeding tube.
- Age of patient and othe medication may impact on kinetic variability.
- Possible side-effects as would be expected from benzodiazepines. Children are more susceptible to sedation and paradoxical emotional reactions.
- Available as: tablets 10 mg (Frisium$^{(R)}$) tablets; (5 mg – unlicensed and available on a named-patient basis); oral liquid (5 mg in 5 ml and 10 mg in 5 ml – care with differing strengths).
- Frisium$^{(R)}$ tablets are NHS black-listed except for epilepsy and endorsed 'SLS'. Schedule 4 CD (CD-Benz).

Evidence: [338, 341, 427-429]

Clonazepam

Use:

- Tonic-clonic seizures
- Partial seizures
- Cluster seizures
- Myoclonus
- Status epilepticus (3rd line, particularly in neonates)
- Neuropathic pain
- Restless legs
- Gasping
- Anxiety and panic
- Oral dysaesthesia in the adolescent
- Has been used in Neonatal units to control severe continuous seizures resistant to other anticonvulsants

Dose and routes:
By mouth *(anticonvulsant doses: reduce for other indications):*

- **Child 1 month–11 months:** Initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 0.5–1 mg at night (may be given in 3 divided doses if necessary).
- **Child 1–4 years:** Initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 1–3 mg at night (may be given in 3 divided doses if necessary)
- **Child 5–11 years:** Initially 500 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6 mg at night (may be given in 3 divided doses if necessary)
- **Child 12–17 years:** Initially 1 mg at night for 4 nights, increased over 2–4 weeks to usual maintenance of 4–8 mg at night (may be given in 3 divided doses if necessary).

For oral dysaesthesia [burning mouth syndrome] rinse with 0.1mg/ml solution

For status epilepticus: (SR)

Continuous subcutaneousinfusion:

- **Child 1 month–17 years:** Starting dose 20-25 micrograms/kg/24 hours
- Maximum starting doses:
  1-5 years: 250 micrograms/24 hours.
  5-12 years: 500 micrograms/24 hours.
- Increase at intervals of not less than 12 hours to 200 micrograms/kg/24hours (maximum 8 mg/24 hours)
- Doses of up to 1.4 mg/kg/24 hours have been used in status epilepticus in PICU environment.

By intravenous injection over at least 2 minutes, or infusion:

- **Neonate:** 100 micrograms/kg intravenous over at least 2 minutes, repeated after 24 hours if necessary (avoid unless no safer alternative). Used for seizures not controlled with phenobarbital or phenytoin.

- **Child 1 month-11 years:** Loading dose 50 micrograms/kg (maximum 1 mg) by IV injection followed by IV infusion of 10 micrograms/kg/hour adjusted according to response; maximum 60 micrograms/kg/hour.
- **Child 12-17 years:** Loading dose 1 mg by IV injection followed by IV infusion of 10 micrograms/kg/hour adjusted according to response.
  maximum 60 micrograms/kg/hour.

Notes

- Licensed for use in children for status epilepticus and epilepsy. Not licensed for neuropathic pain. Tablets licensed in children.
- Not licensed in the UK for SC use.
- Very effective anticonvulsant, usually 3rd line due to side effects and development of tolerance.
- Use lower doses for panic, anxiolysis, terminal sedation, neuropathic pain, and restless legs.
- Do not use in acute or severe respiratory insufficiency unless imminently dying. Be cautious in those with chronic respiratory disease.
- As an anxiolytic/sedative, clonazepam orally is approximately 20 times as potent as diazepam (i.e. 250micrograms clonazepam equivalent to 5 mg diazepam orally).
- Multiple indications in addition to anticonvulsant activity can make clonazepam particularly useful in the palliative care of children with neurological disorders.
- Many children with complex seizure disorders are on twice daily doses and on higher than recommeded dosages.
- Tolerance in longer term use may be managed by 'switching/rotating' benzodiazepines.
- The dose may be increased for short periods of 3-5 days during times of increased seizures e.g. from viral illness.
- Elimination half-life of 20-40 hours means that it may take up to 6 days to reach steady state; there is a risk of accumulation and toxicity with rapid increase of infusion; consider loading dose to reach steady state more quickly.
- Avoid abrupt withdrawal.
- Associated with salivary hypersecretion and drooling.
- For administration via an enteral feeding tube, tablets may be dispersed in at least 30ml water or consider a liquid formulation (especially for fine-bore tubes). Extra flushing with water is required to stop drug adhering to the wall of the tube. There are no specific data relating to jejunal administration. Administer using the above method. Monitor for loss of efficacy or increased side-effects.
- IV formulation may be diluted and given via enteral tube. Flush tube well following administration.
- Stability of diluted clonazepam is up to 12 hours so prescribers should consider 12 hourly infusions.
- Use non-PVC tubing when administering by subcutaneous infusion.
- Compatible with most drugs commonly administered via continuous subcutaneous infusion via syringe driver. Dilute with WFI or NaCl 0.9%.
- Available as: tablets (500 micrograms scored, 2 mg scored); liquid (0.5 mg in 5 mL and 2 mg in 5 mL now available as licensed preparations from Rosemont, but not indicated in children due to high alcohol content; other unlicensed oral liquids are available from specials manufacturers); injection (1 mg/mL unlicensed). CD Schedule 4 (CD-Benz).

Evidence: [338, 339, 375, 396, 427, 430-435]

Clonidine

Uses:

- Anxiety / sedation (prior to procedure)
- Pain / sedation / opioid sparing / prevention of opioid withdrawal effects
- Regional nerve block
- Spasticity / dystonia
- Status dystonicus
- Behavioural symptoms of irritability, impulsiveness, aggression

Doses and routes:

Anxiety / Sedation / Pre-procedure:
Oral / Intranasal /Rectal:

- **Neonate:** 4 micrograms/kg orally (or intranasally, although this does tend to sting and offers little advantage over the oral route), and in doses of 5 micrograms/kg rectally provides adequate sedation.
- **Child >1 month:** 4 micrograms/kg as a single dose.
  (Suggested maximum 150 micrograms single dose).
  If used as premedicant prior to a procedure give 45-60 minutes before.

Pain / Sedation / Opioid sparing / Prevention of opioid withdrawal effects (most experience on PICU):
Oral / IV Bolus:

- **Child >1 month:** Initial dose 1 microgram/kg/dose 3-4 times daily. Increase gradually as needed and tolerated to maximum of 5 micrograms/kg/dose four times a day.

IV infusion: Can also be used as CSCI

- **Neonates from 37 weeks CorGA:<u>(only if ventilated)</u>**
  Initially 0.25 micrograms/kg /hour, increasing in 0.1 microgram/kg/hour increments until adequate sedation achieved. Most will require 1 microgram/kg per hour, but doses up to 2 micrograms/kgper hour are sometimes necessary.
- **Child >1 month:** 0.1-2 micrograms/kg/hour.
  Usual starting doses:
  - **Child <6 months:** 0.4 micrograms/kg/hour
  - **Child >6 months:** 0.6 microgram/kg/hour

For chronic long-term pain, and once an effective oral dose has been established, conversation to transdermal patches can be considered using a patch size that will give a roughly equivalent daily dose of clonidine (see notes below).

Regional nerve block – only in situations where specialist input is available:

- **Child >3 months:** 1-2 micrograms/kg clonidine in combination with a local anaesthetic.

Spasticity / Movement Disorder:
Oral:

- **Child > 1 month:** 1-5 micrograms/kg/dose three times a day. Frequency of dosing may need to be increased and/or alternative route of administration considered if the enteral route is not possible.

Behavioural problems / Tics / Tourette's syndrome:
Oral:

- **Child > 4 years:** Oral: Initial dose of 25 micrograms at night. Increase as necessary after 1-2 weeks to 50micrograms at night. Dose can be further increased by 25 micrograms every 2 weeks to suggested maximum of 5 micrograms/kg/day or 300 micrograms/day

When using patch (for children over 10 kg)

- 2.5 mg clonidine patch delivers 100 micrograms/day
- 5m g clonidine patch delivers 200 micrograms/day
- 7.5 mg clonidine patch delivers 300 micrograms/day

Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application of patch.

If more than 2.5 mg patch to be used i.e.200 micrograms/day, consider using 2 smaller patches to be changed on different days of the week to reduce end of dose effect.

Conversion of patients on IV or oral clonidine:

- For patients on IV/oral dose less than 150 micrograms/day, select the clonidine 2.5mg patch. Then follow IV/oral tapering dose below.
- For patients on IV/oral dose between 150 micrograms and 250 micrograms/day, select the 5 mg clonidine patch.

IV/Oral tapering doses:

- Apply patch on day 1.
- Day 1 give 100% of oral/IV dose
- Day 2 give 50% of oral/IV dose
- Day 3 give 25% oral/IV dose [436]
- Day 4 patient will only need patch

Notes

- Clonidine is a mixed alpha-1 and alpha-2 agonist (mainly alpha-2). Appears to have synergistic analgesic effects with opioids and prevents opioid withdrawal symptoms. Also useful for its sedative effect. Use established in ADHD, behavioural problems and tics.
- Not licensed for use in children.
- Licensed indication of clonidine is for the treatment of hypertension, so reduction in BP is a likely side effect of use. Titrate the dose of clonidine against the symptoms and monitor BP and pulse on starting treatment and after each dose increase.
- When used for longer than a few days, clonidine should be withdrawn slowly on discontinuation, to prevent acute withdrawal symptoms including rebound hypertension.
- Use with caution in those with bradyarrhythmia, Raynaud's or other occlusive peripheral vascular disease.
- Remove patch if having MRI scan as risk of heating up and causing a burn.
- Common side effects include constipation, nausea, dry mouth, vomiting, postural hypotension, dizziness, sleep disturbances, headache.

- Effects of clonidine are abolished by drugs with alpha-2 antagonistic activity e.g. tricyclics and antipsychotic drugs. Antihypertensive effects may be potentiated by other drugs used to lower BP.
- Oral bioavailability 75-100%; generally 1:1 conversion IV: oral is suggested as a starting point (largely adult data. Note: it has been suggested that oral bioavailability may be lower in children [437]).
- Some reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4 micrograms/kg have been used.
- Onset of effect: oral 30-60 mins. Time to peak plasma concentration:
  oral 1.5-5 hours; epidural 20 minutes; transdermal 2 days.
- CSCI can be useful to maintain control of dystonia in difficult cases.
- Clonidine has been used successfully by SC injection and infusion – seek specialist advice.
- Oral solution may be administered via an enteral feeding tube. Alternatively, if the required dose is appropriate to the available tablet strengths, the tablets may be crushed and dispersed in water for administration via an enteral feeding tube. The 25 microgram tablets do not appear to disperse in water as readily as the 100 microgram tablets. IV solution may also be given via the enteral tube. There is no specific information for jejunal administration. Administer as above but observe for any loss of efficacy or increased side effects.
- Chronic conditions – for older children the use of transdermal patches may be considered when an effective oral dose has been established which is great enough to allow an approximate conversion (1:1) to the transdermal route.
- Available as:
  tablets 25 micrograms, 100 micrograms.
  injection150 micrograms/mL.
  transdermal patch
  2.5 mg (=100 micrograms clonidine/day for 7 days),
  5 mg (=200 micrograms clonidine/day for 7 days) or
  7.5 mg (= 300 micrograms clonidine/day for 7 days),
  (Transdermal patches not licensed in UK – available via importation company); oral solution (special) 50 micrograms/mL.

Evidence: [339, 415, 437-459]

Co-danthramer (dantron and poloxamer 188)

Use:

- Constipation in terminal illness only

Dose and routes:
By mouth:
Co-danthramer 25/200 suspension 5 mL = one co-danthramer 25/200 capsule (Dantron 25 mg, poloxamer '188' 200 mg):

- **Child 2–11 years:** 2.5–5mL at night
- **Child 6–11 years:** 1 capsule at night
- **Child 12–17years:** 5–10mL or 1–2 capsules at night. Dosage can be increased up to 10-20 mL twice a day

Strong co-danthramer 75/1000 suspension 5 mL = two strong co-danthramer 37.5/500 capsules:

- **Child 12–17 years:** 5 mL or 1–2 capsules at night.

Notes

- Co-danthramer is made from dantron and poloxamer '188'.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- No longer used in adult palliative care patients due to excoriation of skin around anus.
- Dantron can turn urine red/brown.
- 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.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [337, 338]

Co-danthrusate (Dantron and Docusate Sodium)

Use:

- Constipation in terminal illness only

Dose and routes:
By mouth:
Co-danthrusate 50/60 suspension 5 mL = one co-danthrusate 50/60 capsule (Dantron 50 mg/ Docusate sodium 60 mg)

- **Child 6–11 years:** 5 mL or 1 capsule at night
- **Child 12–17 years:** 5–15 mL or 1–3 capsules at night

Notes

- Not recommended for under 6 years.
- Co-danthrusate is made from dantron and docusate sodium.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- Dantron can turn urine red/brown.
- 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.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [337, 338, 460]

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.

Evidence: [337-339, 396, 461, 462]

Cyclizine

Use:

- Antiemetic of choice forraised intracranial pressure.
- Nausea and vomiting where other more specific antiemetics (metoclopramide,5HT3 antagonists) have failed.

Dose and routes:
By mouth or by slow IV injection over 3–5 min:

- **Child 1 month–5 years:** 0.5–1 mg/kg up to 3 times daily, maximum single dose 25 mg
- **Child 6–11 years:** 25 mg up to 3 times daily

Child 12–17 years: 50 mg up to 3 times dailyBy rectum:

- **Child 2–5 years:** 12.5 mg up to 3 times daily
- **Child 6–11 years:** 25 mg up to 3 times daily
- **Child 12–17 years**: 50 mg up to 3 times daily

By continuous IV or SC infusion: **Some evidence 50% bioavailability when given orally.**

- **Child 1 month-23 months:** 1.5-3 mg/kg over 24 hours (maximum 25 mg/24 hours),
- **Child 2-5 years:** 25-50 mg over 24 hours
- **Child 6–11 years:** 37.5-75 mg over 24 hours
- **Child 12–17 years:** 75-150 mg over 24 hours

NB Care should be taken with subcutaneous or intravenous use of cyclizine, whichis acidic and can cause injection site reactions.

Notes:

- Antihistaminic antimuscarinic antiemetic.
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- Antimuscarinic side-effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Increased sedative effect when given with tricyclics, anxiolytics, MAOI's.
- Increased antimuscarinic effect when given with tricyclics, antimuscarinics, MAOI's
- Theoretically antagonises betahistine, histamine.
- Avoid in patients on midodrine and children with severe liver disease. In severe cardiac failure may cause fall in cardiac output. Increased risk of transient paralysis with intravenous use in patients with neuromuscular disorders.
- Rapid SC or IV bolus can lead to 'lightheadness' –disliked by some and enthralling to others leading to repeated requests for IV cyclizine.
- For CSCI or IV infusion, dilute only with water for injection or 5% dextrose; *incompatible* with 0.9 %NaCland will precipitate.
- 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. There is no specific information for jejunal administration. If this route is used monitor for any loss of efficacy or increased side-effects.
- Available as: tablets (50 mg), suppositories (12.5 mg, 25 mg, 50 mg, 100 mg from 'specials' manufacturers) and injection (50 mg/mL).

Evidence: [338, 345, 463-466]

Dantrolene

Use:
- Skeletal muscle relaxant.
- Chronic severe voluntary muscle spasm or spasticity.

Dose and routes:

The dose of dantrolene should be built up slowly
By mouth:
- **Child 5–11 years:** Initial dose of 500 micrograms/kg once daily; after 7 days increase to 500 micrograms/kg/dose 3 times daily. Every 7 days increase by a further 500 micrograms/kg/dose until response. Maximum recommended dose is 2 mg/kg 3–4 times daily (maximum total daily dose 400 mg).
- **Child 12–17 years:** Initial dose of 25 mg once daily; after 7 days increase to 25 mg 3 times daily. Every 7 days increase by a further 500 microgram/kg/dose until response. Maximum recommended dose is 2 mg/kg 3–4 times daily (maximum total daily dose 400 mg).

Notes:
- Not licensed for use in children.
- Hepatotoxicity risk; consider checking liver function before and at regular intervals during therapy.
- Contraindicated in hepatic impairment: avoid in liver disease or concomitant use of hepatotoxic drugs.
- Can cause drowsiness, dizziness, weakness, nausea and diarrhoea.
- Cautious use in patients with impaired cardiac or pulmonary function: side effects include pericarditis, pleural effusion, respiratory depression, exacerbation of cardiac insufficiency, tachycardia and blood pressure changes.
- Available as: capsules (25 mg, 100 mg), oral suspension (extemporaneous formulation 5 mg/mL).

Evidence: [338, 371, 372, 376, 467, 468]

Dexamethasone

Use:

Dexamethasone has a wide range of potential uses associated with its capacity to reduce inflammation. They include:

- Headache associated with raised intracranial pressure caused by a tumour.
- Anti-inflammatory in brain and other tumours which cause pressure on nerves or bone or obstruction of hollow viscus.
- Analgesic role in nerve compression, spinal cord compression and bone pain.
- Antiemetic either as an adjuvant or in highly emetogenic cytotoxic therapies.

Dose and routes
Prescribe as dexamethasone base.

Headache associated with raised intracranial pressure
By mouth or IV:
Child 1 month–12 years: 250 micrograms/kg twice a day for 5 days; then reduce or stop.

To relieve symptoms of brain or other tumour
Numerous other indications in cancer management such as spinal cordand/or nerve compression, some causes of dyspnoea, bone pain, superior vena caval obstruction etc,, only in discussion with specialist palliative medicine team.High doses >16 mg/24 hrs may be advised.

Antiemetic
By mouth or IV:

- **Child < 1 year:** Initial dose 250 micrograms 3 times daily. This dose may be increased as necessary and as tolerated up to 1mg 3 times daily
- **Child 1–5 years:** Initial dose 1 mg 3 times daily. This dose may be increased as necessary and as tolerated up to 2 mg 3 times daily
- **Child 6–11 years:** Initial dose 2 mg 3 times daily. This dose may be increased as necessary and as tolerated up to 4 mg 3 times daily
- **Child 12–17 years:** 4 mg 3 times daily

Notes:

- The adverse effects of dexamethasone quickly outweigh its benefits. Ideally it should be given as short courses of 48 hours or five days, but that is not always possible in the palliative phase, and many patients find themselves on dexamethasone for long periods.
- Dexamethasone can be stopped abruptly if it has been given for less than two weeks, but otherwise should be weaned down over a number ofweeks to allow recovery of the hypo-pituitary axis and avoid an Addisonian crisis.
- Not licensed for use in children as an anti-emetic.
- Dexamethasone has high glucocorticoid activity but relatively insignificant mineralocorticoid activity so is particularly suited for high dose anti-inflammatory therapy.
- Dexamethasone can be given in a single daily dose each morning for most indications. Whether in a single dose or two divided doses, giving the total daily dose of dexamethasone before midday reduces the likelihood of corticosteroid induced insomnia and agitation.

- Dexamethasone has an oral bioavailability of >80%; it can be converted to SC or IV on a 1:1 basis.
- Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg.
- Dexamethasone 1 mg = 7 mg prednisolone (anti-inflammatory equivalence).
- Dexamethasone has a long duration of action.
- Problems of weight gain and Cushingoid appearance are major concerns specifically in children. All specialist units therefore use pulsed dose regimes in preference to continual use. Regimes vary with conditions and specialist units. Seek local specialist advice.
- Other side effects include diabetes, osteoporosis, muscle wasting, peptic ulceration and behavioural problems and agitation, also extreme exacerbation of and lability of mood (tearfulness, physical aggression).
- Tablets may be dispersed in water if oral liquid unavailable. Oral solution or tablets dispersed in water may be administered via an enteral feeding tube.
- Available as: tablets (500 micrograms, 2 mg), soluble tablets 2 mg, 4 mg, 8 mg, oral solution (2 mg/5 mL 10 mg/5 mL and 20 mg/5 mL and injection as dexamethasone sodium phosphate (equivalent to 3.8 mg/mL dexamethasone base or 3.3 mg/mL dexamethasone base.

Evidence: [208, 341, 469-472]

Diamorphine

Use:

- Moderate to severe pain.
- Dyspnoea

Dose and routes:

As background opioid for chronic pain
Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in opioid naive patient. The maximum dose stated applies to **starting** dose only.

By continuous subcutaneous or intravenous infusion

- **Neonate:** Initial dose of 60 micrograms/kg/24 hours which can be increased as necessary to a suggested maximum of 150 micrograms/kg/24 hours
- **Child 1 month-18 years:** 50-600 micrograms/kg/ 24 hours (initial maximum 10 mg/24 hours) adjusted according to response

By IV /SC or IMinjection:

- **Neonate:**15 micrograms/kg every 6 hours as necessary, adjusted according to response
- **Child 1-2 months:** 20 micrograms/kg every 6 hours as necessary, adjusted according to response
- **Child 3-5 months:** 25-50 micrograms/kg every 6 hours as necessary, adjusted according to response
- **Child 6-11 months:** 75 micrograms/kg every 4 hours as necessary, adjusted according to response
- **Child 1-11 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5 mg
- **Child 12-17 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5-5 mg.

By intranasal or buccal route:

- **Neonate:** 50 micrograms/kg/dose every 6-8 hours
- **Child over 10 kg**: 50-100 micrograms/kg every 4 hours as necessary adjusted according to response; maximum single dose 10 mg.

Injection solution can be used by intranasal or buccal routes or Nasal spray (Ayendi(R)) now available and licensed for use in children aged 2 years and over (weight 12 kg upwards) for the management of severe acute pain.

720 micrograms/actuation (Ayendi(R))

- 12-17 kg: 2 sprays as a single dose
- 18-23 kg: 3 sprays as a single dose
- 24-29 kg: 4 sprays as a single dose

1600 micrograms/actuation (Ayendi(R))

- 30-39 kg: 2 sprays as a single dose
- 40-49 kg: 3 sprays as a single dose

Intermittent pain without background opioids

Buccal, IV or SC route

- 30 micrograms/kg 1–4 hrly as needed.

Breakthrough pain

By buccal, subcutaneous or IV routes

- For breakthrough pain use 10-16% of total daily diamorphine dose every 1-4 hours as needed.
- Contact the medical palliative team if someone has needed three doses consecutively as they will need a review of their pain control.

Dyspnoea

By buccal, subcutaneous or IV routes

- **Neonates:** 10 micrograms/kg/dose
- **Child 1 month-11 years:** Dose as for pain, but at 25-50% of breakthrough dose

Notes:

- Diamorphine injection is licensed for the treatment of children who are terminally ill.
- For intranasal or buccal administration of diamorphine use the injection powder reconstituted in water for injections (unlicensed route of administration) or the nasal spray may be used (licensed for use in the management of severe acute pain from 2 years of age).
- In neonates, dosage interval should be extended to 6 or 8 hourly depending on renal function and the dose carefully checked, due to increased sensitivity to opioids in the first year of life.
- In poor renal function, dosage interval may be lengthened, or opioids only given as required and titrated against symptoms. Consider changing to fentanyl.
- For CSCI usually dilute with water for injections, as concentration-related incompatibility occurs at high doses with 0.9% saline (if above diamorphine 40 mg/ml).
- Diamorphine can be given by subcutaneous infusion up to a concentration of 250 mg/mL.
- Morphine injection is rapidly taking over from diamorphine, as the only benefit of diamorphine over morphine is its better solubility when high doses are needed and this is rarely a problem in paediatric doses.
- Spray has a significant volume and shelf life is very short. Thiscan make the spray difficult to use in practice.
- Available as: injection (5 mg, 10 mg, 30 mg, 100 mg, 500 mg ampoules); nasal spray 720 micrograms/actuation and 1600 micrograms/actuation (Ayendi Nasal Spray$^{(R)}$).
- Schedule 2 CD.

Evidence: [190, 337, 338, 341, 396, 473, 474]

Diazepam

Use:

- Short term anxiety relief
- Agitation
- Panic attacks
- Relief of muscle spasm
- Treatment of status epilepticus.

Dose and routes

Short term anxiety relief, panic attacks and agitation

By mouth:

- **Child 2–11 years:** 0.5-2 mg 3 times daily
- **Child 12–18 years:** Initial dose of 2 mg 3 times daily increasing as necessary and as tolerated to a maximum of 10 mg 3 times daily.

Relief of muscle spasm

By mouth:

- **Child 1–11 months:** Initial dose of 250 micrograms/kg twice a day
- **Child 1–4 years:** Initial dose of 2.5 mg twice a day
- **Child 5–11 years:** Initial dose of 5m g twice a day
- **Child 12–17 years:** Initial dose of 10 mg twice a day; maximum total daily dose 40mg.

Status epilepticus

By IV injection over 3–5minutes:

Neonate: 300-400 micrograms/kg as a single dose repeated once after 10 minutes if necessary
Child 1 month–11 years: 300-400 micrograms/kg (max 10 mg) repeated once after 10 minutes if necessary
Child 12–17 years: 10 mg repeated once after 10 minutes if necessary.

By rectum (rectal solution):

- **Neonate:** 1.25–2.5 mg repeated once after 10 minutes if necessary
- **Child 1 month–1 year:** 5 mg repeated once after 10 minutes if necessary
- **Child 2–11 years:** 5–10 mg repeated once after 10 minutes if necessary
- **Child 12–17 years:** 10-20 mg repeated once after 10 minutes if necessary.

Notes

- Do not use in acute or severe respiratory insufficiency unless in the imminently dying.
- Rectal tubes not licensed for children < 1 year old.
- Use with caution in mild-moderate hepatic diseaseand children with muscle weakness, respiratory depression or sleep apnoea.
- Metabolised via the cytochrome P450 group of liver enzymes: – potential for interaction with any concurrent medicine that induces or inhibits this group of enzymes. Enhancement of the central depressive effect may occur if diazepam is combined with drugs such as neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates or sedative antihistamines.
- Can cause dose-dependent drowsiness and impaired psychomotor and cognitive skills.

- Almost 100% bioavailable when given orally or by rectal solution.
- Onset of action: apprx 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.
- The oral solution may be administered via a gastrostomy tube. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.
- Available as: tablets (2 mg, 5 mg, 10 mg), oral solution/suspension (2 mg/5 mL, 5 mg/5 mL), rectal tubes (2.5 mg, 5 mg, 10m g), and injection (5 mg/mL solution and 5 mg/mL emulsion).Schedule 4 (CD Benz).

Evidence: [59, 63, 65, 337, 338, 341, 345, 371, 376, 431, 475-477]

Diclofenac Sodium

Use:

- Mild to moderate pain and inflammation, particularly musculoskeletal disorders.

Dose and routes
By mouth or rectum:

- **Child 6 months-17 years:** Initial dose of 0.3 mg/kg 3 times daily increasing if necessary to a maximum of 1 mg/kg 3 times daily (maximum 50mg single dose).

By IV infusion:

- **Child 2–17 years:** 0.3-1 mg/kg 1–2 times daily; maximum of 150 mg/day and for a maximum of 2 days.

Notes:
Will cause closure of ductus arteriosus; contraindicated in duct-dependent congenital heart disease

- Not licensed for use in children under 1 year; *suppositories* not licensed for use in children under 6 years (except for use in children over 1 year for juvenile idiopathic arthritis); solid dose forms containing more than 25mg not licensed for use in children; injection (IV infusion only) not licensed for use in children.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use. However, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects: piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk).
- Use with caution in children with cardiac, hepatic or renal impairment and those with asthma.
- Smallest dose that can be given practically by rectal route is 3.125 mg by cutting a 12.5 mg suppository into quarters (CC).
- For IV infusion, dilute in 5% glucose or 0.9% NaCl (previously buffered with sodium bicarbonate) and infuse over 30-120 minutes.
- Available as: gastro-resistant tablets (25 mg, 50 mg), modified-release tablets (25 mg, 50 mg, and 75 mg), modified release capsules (75 mg and 100 mg), injection (25 mg/mL Voltarol^{R} for IV infusion only), and suppositories (12.5 mg, 25 mg, 50 mg and 100mg).

Evidence: [338, 341, 345, 420]

Dihydrocodeine

Use:

- Alternative to low dose morphine on WHO pain ladder, mild to moderate pain in patients known to be able to benefit. Step 2 pain (i.e. moderate and/or intermittent) that is opioid sensitive.

Dose and routes:
By mouth or deep subcutaneous or intramuscular injection:

- **Child 1-3 years:** 500 micrograms/kg every 4-6 hours
- **Child 4-11 years:** Initial dose of 500 micrograms/kg (maximum 30 mg/dose) every 4-6 hours. Dose may be increased if necessary to 1 mg/kg every 4-6 hours (Maximum 30 mg/dose)
- **Child 12-17 years:** 30 mg (maximum 50 mg by intramuscular or deep subcutaneous injection) every 4-6 hours. Oral doses up to 40-80 mg 3x daily can be given (maximum 240 mg/day).
- Modified release tablets used 12 hourly (use ½ of previous total daily dose for each modified release dose). For children age 12-18 years doses up to 60-120 mg every 12 hours can be given.

Notes:

- Most preparations not licensed for children under 4 years.
- Potency around one fifth of oral morphine (OME 0.2).
- Relatively constipating compared with morphine / diamorphine.
- Dihydrocodeine is itself an active substance, not a pro-drug.
- Oral bioavailability 20%, so probably equipotent with codeine by mouth (but opinion varies). Twice as potent as codeine by injection.
- Time to onset of action 30 minutes, duration of action 4 hours for immediate release tablets.
- Side effects as for other opioids, plus paralytic ileus, abdominal pain, paraesthesia.
- Precautions: avoid or reduce dose in hepatic or renal failure.
- Oral solution may be administered via an enteral feeding tube. Dilute with an equal volume of water before administration.
- Available as: tablets (30mg, 40mg), oral solution (10 mg/5 mL), injection (Schedule 2 CD), (50 mg/mL 1 mL ampoules) and m/r tablets (60 mg, 90 mg, 120 mg). Other than the injection, other forms of dihydrocodeine are CD Schedule 5 (CDInv).

Evidence: [338, 340, 396, 420] ARE, NoRE for injection

Docusate

Use:

- Constipation (faecal softener).

Dose and routes
By mouth:

- **Child 6 months–1 year:** Initial dose of 12.5 mg 3 times daily; adjust dose according to response
- **Child 2–11 years:** Initial dose of 12.5 mg 3 times daily. Increase to 25 mg 3 times daily as necessary and then further adjust dose according to response
- **Child 12–17 years:** Initial dose 100 mg 3 times daily. Adjust as needed according to response up to 500 mg/day in divided doses.

By rectum:

- **Child 12–17 years:** 1 enema as single dose.

Notes:

- Adult oral solution and capsules not licensed in children < 12 years.
- Oral preparations act within 1–2 days.
- Rectal preparations act within 20mins.
- Mechanism of action is emulsifying, wetting and mild stimulant.
- Stimulant laxatives should be avoided in intestinal obstruction.
- For administration by mouth, solution may be mixed with milk or squash. Oral solution may be administered via an enteral feeding tube. Administration directly into the jejunum will not affect the pharmacological response.
- Doses may be exceeded on specialist advice.
- Available as capsules (100 mg), oral solution (12.5 mg/5 mL paediatric, 50 mg/5 mL adult), and enema (120 mg in 10 g single dose pack).

Evidence: [338]

Domperidone

MHRA April 2014: Domperidone is associated with a small increased risk of serious cardiac side effects. Its use is now restricted to the relief of symptoms of nausea and vomiting and the dosage and duration of use have been reduced.
Domperidone is now **contraindicated** for use in those with underlying cardiac conditions and other risk factors.
The use of domperidone in palliative care is excluded from these recommendations HOWEVER caution should be exercised, nevertheless.

The indications and doses below are therefore largely unlicensed usage in a particular population. Use the minimum effective dose. Do not use in those with known cardiac problems or other risk factors.

Obtain ECG prior to starting and follow QTc interval to ensure safety.

Use:

- Nausea and vomiting where poor GI motility is the cause.
- Gastro-oesophageal reflux resistant to other therapy.

Dose and routes
For nausea and vomiting
By mouth:

- **Neonates:** 250 micrograms/kg 3 times a day increase if necessary to 400 micrograms/kg 3 times a day
- **Child >1 month and body-weight ≤ 35 kg:** Initial dose of 250 micrograms/kg 3–4 times daily increasing if necessary to 500 micrograms/kg 3-4 times daily. Maximum
- 2.4 mg/kg (or 80 mg) in 24 hours
- **Child of body-weight> 35 kg:** Initial dose of 10 mg 3-4 times daily increasing if necessary to 20 mg 3-4 times daily. Maximum 80 mg in 24 hours

For gastro-oesophageal reflux and gastrointestinal stasis
By mouth:

- **Neonate:** Initial dose of 100 micrograms/kg 4–6 times daily before feeds. Dose may be increased, if necessary, to maximum of 300 micrograms/kg 4-6 times daily
- **Child 1 month–11 years:** Initial dose of 200 micrograms/kg (maximum single dose 10mg) 3-4 times daily before food. Dose may be increased, if necessary, to 400 micrograms/kg 3-4 times daily. Maximum single dose 20 mg
- **Child 12–17 years:** Initial dose of 10 mg 3–4 times daily before food. Dose may be increased, if necessary, to 20 mg 3-4 times daily

Notes

- Domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- Domperidone is contraindicated in those:
  - With conditions where cardiac conduction is, or could be, impaired
  - With underlying cardiac diseases such as congestive heart failure

  - Receiving other medications known to prolong QT interval(e.g. erythromycin, ketoconazole) or which are potent CYP3A4 inhibitors
  - With severe hepatic impairment
- This risk may be higher with daily doses greater than 30 mg. Use at lowest effective dose.
- Not licensed for use in gastro-intestinal stasis; not licensed for use in children for gastro-oesophageal reflux disease.
- Reduced ability to cross blood brain barrier, so less likely to cause extrapyramidal side effects compared with metoclopramide.
- Promotes gastrointestinal motility so diarrhoea can be an unwanted (or useful) side effect.
- Not to be used in patients with hepatic impairment.
- For administration via an enteral feeding tube: Use the suspension formulation, although the total daily dose of sorbitol should be considered. If administering into the jejunum, dilute the suspension with at least an equal volume of water immediately prior to administration.
- Available as: tablets (10 mg), oral suspension (5 mg/5 mL).

Evidence: [89, 91, 93, 204, 206, 338, 339, 341, 345, 478]

Entonox *(nitrous oxide)*

Use:

- As self-regulated analgesia without loss of consciousness.
- Particularly useful for painful dressing changes.

Dose and routes
By inhalation:

- **Child:** Up to 50% to be administered using suitable anaesthetic apparatus in oxygen adjusted according to the patient's needs. Self-regulated usually over 5 years of age.

Notes:

- Is normally used as a light anaesthesic.
- Rapid onset and then offset.
- Should only be used as self-administration using a demand valve; all other situations require a specialist paediatric anaesthetist.
- Use is dangerous in the presence of pneumothorax or intracranial air after head injury.
- Hypoxia can occur immediately after administration so additional oxygen should always be given for several minutes following administration.
- Avoid concomitant use with methotrexate as can increase antifolate effect.
- Risk of enhanced hypotensive effect with a number of medications.
- Prolonged use can cause megaloblastic anaemia. Consider assessment of plasma vitamin B12 concentration in children at risk of deficiency.
- Nitrous oxide 1ml per 1ml various sizes of cylinders available from medical gas suppliers Linde GasUK and BOC Ltd. See BNFC for additional information.
- May be difficult to make available in hospice settings especially if needed infrequently, due to training, governance and supply implications.

Evidence: [338, 479-481]

Erythromycin

Use:

- Gastrointestinal stasis (motilin receptor agonist).

Dose and routes
By mouth or by intravenous infusion:

- **Neonate:** 3 mg/kg 4 times daily
- **Child 1 month–17 years:** 3 mg/kg 4 times daily
- **Adult:** 250-500 mg 3 times daily

Notes:

- Not licensed for use in children with gastrointestinal stasis.
- Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents.
- Erythromycin is a known inhibitor of the cytochrome P450 system and may increase the serum concentration of drugs which are metabolised by this system. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Care should be taken with medications known to prolong the QT interval of the electrocardiogram.
- For administration via enteral feeding tube use the suspension. Dilute the suspension with an equal volume of water before administration.
- Absorbed in small intestine so no concerns with jejunal administration.
- Available as: tablets (250 mg, 500 mg) and oral suspension (125 mg/5 mL,
- 250 mg/5 mL, 500 mg/5 mL).

Evidence: [23, 338, 482] WRE

Etoricoxib

Uses:

- Anti-inflammatory analgesic; adjuvant for musculoskeletal pain

Dose and route:
Oral:

- **Child 12-15 years:** Initial dose of 30 mg once daily. Dose may be increased as necessary and as tolerated to a maximum of 60 mg once daily
- **Child 16 years and older:** Usual dose of 30-60 mg once daily. Doses of 90 mg daily may be used on a short term basis until symptoms controlled then attempt to reduce back to 60 mg daily. Doses up to 120 mg have been used on a short-term basis in acute gouty arthritis in adults.

Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.
- Etoricoxib is not licensed for use in children less than 16 years of age. The pharmacokinetics of etoricoxib in children less than 12 years of age has not been studied.
- Etoricoxib may mask fever and other signs of inflammation.
- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID or in those with a coagulation disorder. However, etoricoxib may be better tolerated than other NSAIDs in patients with known hypersensitivity.
- Etoricoxib is contraindicated in those with active peptic ulceration or active GI bleeding; severe hepatic or renal dysfunction; inflammatory bowel disease or congestive heart failure.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. All NSAIDs are associated with GI toxicity. In adults' evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects with piroxicam and ketorolac associated with the highest risk and ibuprofen at low to medium dose with the lowest risk. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur.
- 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; ALT increased, AST increased; ecchymosis; asthenia/fatigue, flu-like disease.
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Etoricoxib does NOT appear to inhibit or induce CYP isoenzymes. However, the main pathway of etoricoxib metabolism is dependent on CYP enzymes (primarily CYP3A4) so co-administration with drugs that are inducers or inhibitors of this pathway may affect the metabolism of etoricoxib.
- Etoricoxib tablets may be dispersed in 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. There are no specific data relating to the jejunal administration of etoricoxib. Administer as above and monitor for lack of efficacy or increased side-effects.
- Available as: film coated tablets 30 mg, 60 mg, 90 mg, 120 mg. Tablets contain lactose.

Evidence: [337, 483, 484] SR EA

Fentanyl

Use:

- Step 2 WHO pain ladder (moderate to severe pain).

Dose and routes

Normally convert using oral morphine equivalent (OME) from previous analgesia.

Use the following **starting** doses in the opioid naive patient. The maximum dose stated applies to **starting** dose only.

MHRA/CHM advice: Transdermal fentanyl patches: life-threatening and fatal opioid toxicity from accidental exposure, particularly in children (October 2018)

Accidental exposure to transdermal fentanyl can occur if a patch is swallowed or transferred to another individual. Always fully inform patients and their carers about directions for safe use of fentanyl patches, including 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.

•ensuring that old patches are removed before applying a new one.

•following instructions for safe storage and properly disposing of used patches or those which are not needed.

Patients and carers should be advised to seek immediate medical attention if overdose is suspected—see Side-effects and Patient and carer advice for further information.

By transdermal patch or continuous infusion:

- Based on oral morphine dose equivalent (given as 24-hour totals).

72-hour Fentanyl patches are *approximately* equivalent to the following 24 hour doses of oral morphine

morphine salt 30 mg daily ≡ fentanyl '12' patch
morphine salt 60 mg daily ≡ fentanyl '25' patch
morphine salt 120 mg daily ≡ fentanyl '50' patch
morphine salt 180 mg daily ≡ fentanyl '75' patch
morphine salt 240 mg daily ≡ fentanyl '100' patch

By oromucosal application (lozenge with oromucosal applicator)

- **Child 2-18 years and greater than 10 kg:** 15 micrograms/kg as a single dose, titrated to a maximum dose 400micrograms (higher doses under specialist supervision).

By intranasal (starting doses for opioid naïve patients and acute pain)

- **Neonate - Child<2 years:** 1 microgram/kg as a single dose
- **Child 2-18 years:** 1-2 micrograms/kg as a single dose, with initial maximum single dose of 50 micrograms

By continuous intravenous/subcutaneous infusion

- **Neonate or infant:** 0.15-0.5 micrograms/kg/ hour
- **Child:** 0.25-1 microgram/kg/hour

By intravenous/subcutaneous injection (lower doses are required in non-ventilated neonatesand opioid naïve patients)

- **Neonate or infant:**
  - **Non-ventilated:** 0.15-0.25 micrograms/kg per dose slowly over 3-5 minutes; repeated 30-60 minutes
  - **Ventilated:** 0.25-0.5 micrograms/kg per dose slowly over 3-5 minutes; repeated every 30-60 minutes
- **Child over 1 year:** 0.25–0.5 micrograms/kg per dose, slowly over 3-5 minutes, repeated every 30-60 minutes.

Notes:

- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.
- In neonatology there is no lower CorGA as fentanyl is used for endotracheal intubation at all gestations.
- Can be safely used in poor, deteriorating or absent renal function.
- Avoid or reduce dose in hepatic impairment.
- Synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.
- Evidence that it is less constipating than morphine has not been confirmed in more recent studies[485].
- Consider reducing starting doses in obese children – to use ideal body weight rather than actual body weight.
- 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.
- For break through pain, fentanyl effect is idiosyncratic: start at significantly lower doses than the equivalent for oral morphine. Always start at lower doses then titrate up.

Intranasal

- Intranasal route works more quickly and is shorter lasting than oromucosal.
- Pharmacokinetics of fentanyl intranasally arefavourable but it isnot always practical and/or well tolerated in children.
- Intranasal route has also been used for management of respiratory distress in paediatric palliative care.
- Injection solution can be administered by the intranasal route for doses less than 50micrograms which is the lowest strength of nasal spray available.
- Injection solution can be administered drop wise via nasal route (may be unpleasant) or using an atomiser device such as that used by A+E units for intranasal diamorphine.

Lozenges

- The usefulness of lozenges and buccal/sublingual tablets in children is limited by the dose availability andno reliable conversion factor. In practice this also varies between preparations and between individuals.
- Another caution is that oral morphine approximate equivalence of the smallest lozenge (200 micrograms) is 30 mg, meaning it is probably suitable to treat breakthrough pain only for children receiving a total daily dose equivalent of 180mg morphine or more.
- Older children will often choose to remove the lozenge before it is completely dissolved, giving them some much-valued control over their analgesia.
- The lozenge must be rotated in buccal pouch, not sucked.

Fentanyl transdermal patches

- The patch formulation is not usually suitable for the initiation or titration phases of opioid management in palliative care since the patches represent large dose incrementsand because of the time lag to achieve steady state.
- Fentanyl patches takes up to 17 hours to reach steady state. Commence fentanyl patch with last dose of slow-release morphine.
- Fentanyl patches should be changed every 72 hours and the site of application rotated. In some children who are rapid metabolisers the patch may not last for 72 hours and the patches may need to be changed every 36-48 hours.
- Conversion ratio is 1:1 for transdermal fentanyl to intravenous/ subcutaneous routes.
- A reservoir of fentanyl accumulates in the body, and significant blood concentrations persist for at least 24 hours after discontinuing transdermal fentanyl. It takes 17 hours or more for the plasma-fentanyl concentration to decrease by 50%; replacement opioid therapy should therefore be initiated at a low dose and increased gradually.
- For rapidly escalating symptoms in the last few hours and days of life, continue transdermal fentanyl and give additional SC morphine PRN. If >2 PRN doses are required in 24 hours, give morphine by continuous subcutaneous infusion, while continuing transdermal fentanyl, starting with a dose equal to the sum of the PRN doses over the preceding 24 hours. If necessary, adjust the PRN dose considering the total opioid dose (i.e. transdermal fentanyl + continuous subcutaneous morphine).

Formulations

- Intranasal spray Instanyl® (50 micrograms/metered spray, 100micrograms/metered spray and 200 micrograms/metered spray). PecFent® (100 micrograms/metered spray and 400 micrograms/metered spray).
  Lozenge with oromucosal applicator Actiq® (200 micrograms, 400 micrograms,600 micrograms, 800 micrograms, 1.2 mg and 1.6 mg).
  Sublingual/buccal tablets Abstral(® (100, 200, 300, 400, 600 and 800 micrograms) Recivit® (133, 267, 400 and 800 micrograms) and buccal tablets Effentora(®) (100, 200, 400, 600 and 800 micrograms); Breakyl(®) (200, 400, 600, 800 and 1200 micrograms).
  Patches: various manufacturers (12 micrograms/hour, 25 micrograms/hour, 50 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour); Ionys® transdermal system (40 microgram/dose)
  Injection: 50 microgram per mL
- Schedule 2 CD

Evidence: [39, 235, 338, 340, 348, 473, 486-508]

Fluconazole

Use:

- Mucosal candidiasis infection, invasive candidal infections or prevention of fungal infections in immunocompromised patients.

Dose and routes

Mucosal candidal infection

By mouth or intravenous infusion:

- **Neonate up to 13 days:** 3-6 mg/kg on first day then 3 mg/kg every 72 hours
- **Neonate 14-28 days-:** 3-6 mg/kg on first day then 3 mg/kg every 48 hours
- **Child 1 month–11 years:** 3-6 mg/kg on first day then 3 mg/kg (maximum 100 mg) daily
- **Child 12–17 years:** 50 mg/day. Increase to 100 mg/day in difficult infections.

Invasive candidal infections and cryptococcal infections

By mouth or intravenous infusion:

- **Neonate up to 13 days**: 6-12 mg/kg every 72 hours
- **Neonate 14-28 days**: 6-12 mg/kg every 48 hours
- **Child 1 month–17 years**: 6-12 mg/kg (max.800mg) every 24 hours

Prevention of fungal infections in immunocompromised patients

By mouth or intravenous infusion

- **Neonate up to 13 days**: 3-12 mg/kg every 72 hours
- **Neonate 14-28 days:** 3-12 mg/kg every 48 hours
- **Child 1 month–17 years:** 3-12 mg/kg (max.400 mg) every 24 hours

Notes:

- Use for 7-14 days in oropharyngeal candidiasis.
- Usefor14-30 days in other mucosal infections.
- Different duration of use in severely immunocompromised patients.
- Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.
- The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.
- For intravenous infusion, give over 10–30 minutes; do not exceed an infusion rate of 5–10mL/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.
- Available as: capsules (50 mg, 150 mg, 200 mg); oral suspension (50 mg/5 mL, 200 mg/5 mL) and IV infusion (2 mg/mL in 50 mL, 100 mL or 200 mL infusion bags).

Evidence: [338, 345, 509, 510]

Fluoxetine

Use:

- Major depression.

Dose and routes
By mouth:

- **Child 8–17 years:** Initial dose 10 mg once a day. May be increased after 1-2 weeks if necessary to a maximum of 20 mg once daily.

Notes:

- Licensed for use in children from 8 years of age.
- Use with caution in children, ideally with specialist psychiatric advice.
- Increased risk of anxiety for first 2 weeks.
- Onset of benefit 3-4 weeks.
- Consider long half-life when adjusting dosage. Do not discontinue abruptly.
- May also help for neuropathic pain and intractable cough.
- Suicide related behaviours have been more frequently observed in clinical trials among children and adolescents treated with antidepressants compared with placebo. Mania and hypomania have been commonly reported in paediatric trials.
- The most reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.
- Because the metabolism of fluoxetine, (like tricyclic antidepressants and other selective serotonin re-uptake inhibitors), involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions.
- Must not be used in combination with a MAOI.
- Oral liquid may be administered via NG tube or gastrostomy. There are no specific reports of jejunal administration of fluoxetine. Monitor for loss of efficacy or increased side-effects.
- Available as: capsules (20 mg, 60 mg), dispersible tablets (20 mg) and oral liquid (20 mg/5 mL).

Evidence: [293-295, 337, 338, 511-515]

Gabapentin

Important safety information

The levels of propylene glycol, acesulfame K and saccharin sodium may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rosemont brand) are given to adolescents or adults with low body-weight (39–50 kg)—consult product literature.

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.

Use:

- Adjuvant in neuropathic pain
- Neuroirritability
- Visceral hyperalgesia
- Third line management of abnormal tone and movement disorders in cerebral palsy
- Epilepsy

Dose and routes

Epilepsy
Consult BNFc or local neurology protocols

Neuropathic pain
By mouth:

- **Neonate-Child 1 year:** 5 mg/kg given as below
- **Child 2 -11 years:** 5-10 mg/kg given as below
  - Day 1 – give 5-10 mg/kg as a single dose (maximum single dose 300 mg),
  - Day 2 – give 5-10 mg/kg twice daily (maximum single dose 300 mg),
  - Day 3 onwards, give 5-10 mg/kg three times daily (maximum single dose 300 mg),
  - Increase further if necessary to maximum of 20 mg/kg/dose (maximum single dose 600 mg). See notes for day 3 onward titration regimes.
- **From 12 years:** Initially 300 mg once daily for day 1, then 300 mg twice daily for day 2, then 300 mg 3 times a day for day 3, then increase in steps of 300 mg every 3-7 days given in 3 divided doses daily. The maximum daily dose can be increased according to response to a maximum of 3600 mg/day.

Gabapentin to Pregabalin Switch for neuropathic pain
Consult appendix 3

Notes:

- Not licensed for neuropathic pain in children. Although does have a license as an adjunct for the treatment of focal seizures for those >6 years (maximum licensed dose 50 mg/kg/day if < 12 years) and as a monotherapy for the treatment of focal seizures in those >12 years.
- Patient Information; Medicines for Children Leaflets are available for gabapentin used for both neuropatheic pain and seizures: www.medicinesforchildren.org.uk/gabapentin-for-neuropathic-pain
  www.medicinesforchildren.org.uk/gabapentin-for-preventing-seizures
- Speed of titration after first 3 days of initiation varies between:
  - fast regime, increase every 3 days;
  - slow regime (for debilitated children or when taking other CNS depressants),to increase every one to two weeks.
- No consensus on dose for neuropathic pain. Doses shown are based on doses for partial seizures and authors' experience.
- Gabapentin and pregabalin are a similar class of drug. Evidence from pre-clinical studies in animals suggest that both the anti-seizure and analgesic activity of gabapentin as with pregabalin 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.
- Absolute bioavailability of a 300 mg gabapentin capsule is approximately 60%. However, unlike pregabalin which shows linear pharmacokinetics, gabapentin absorption is saturable, leading to a non-linearpharmacokinetic profile accounting for the decrease in bioavailability seen with increasing gabapentin dose and variations in bioavailability in patient populations. Careful titration of dose is required.
- Peak plasma concentrations occur 2-3 hours after oral dosing.
- Food does not affect gabapentin bioavailability. However co-administration with antacids containing aluminium and magnesium can reduce bioavailability by up to 24%. Manufacturers recommend giving gabapentin two hours after antacids.
- Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or opioids should be reduced as clinically appropriate.
- Gabapentin is solely excreted unchanged by the kidneys. Therefore dose reduction is required in renal impairment (consult manufacturer's literature), but not in hepatic impairment.
- Very common (>1 in 10) side-effects: somnolence, dizziness, ataxia, viral infection, fatigue, fever.
- NICE Guidance CG173 (Neuropathic pain in adults) recommends: 'offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment of neuropathic pain. If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs and consider switching again if the second and third drugs tried are also not effective or not tolerated'.
- Public Health England issued a warning to prescribers in December 2013, stating that pregabalin and gabapentin had potential for creating dependence and that they may be misused in certain situations. From April 2019 gabapentin has been reclassified as a Schedule 3 controlled drug.

- Adult evidence for use in pruritis in ureamia, anxiety, hot flushes, sweating, refractory hiccups, restless legs syndrome and refractory cough.
- Capsules can be opened but have a bitter taste.
- 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. There are no specific data relating to jejunal administration of gabapentin. Administer using the above method. Monitor for loss of efficacy or increased side-effects.
- Available as: capsules (100 mg, 300 mg, 400 mg); tablets (600 mg, 800 mg), oral solution 250 mg/5 mL (Neurontin, United States import).
- Schedule 3 controlled drug but exempt from safe custody requirements.

Evidence: [337, 338, 345, 394, 396, 516-536] NoRE, WRE

Gaviscon®

Use:

- Gastro-oesophageal reflux, dyspepsia and heartburn.

Dose and routes
By mouth:

- **Neonate–2 years, body weight < 4.5 kg:** 1 dose (half dual sachet) when required mixed with feeds or with water for breast fed babies, maximum 6 doses in 24hours
- **Neonate–2 years, body weight > 4.5 kg:** 2 doses (1 dual sachet) when requiredmixed with feeds or with water for breast fed babies or older infants, maximum 6 doses in 24hours

Gaviscon Liquid and Tablets

- **Child 2-11 years:** 1 tablet or 5-10 mL liquid after meals and at bedtime
- **Child 12-17 years:** 1-2 tablets or 10-20mL liquid after meals and at bedtime

Gaviscon Advance

- **Child 2-11 years:** 1 tablet or 2.5-5mL suspension after meals and at bedtime (under medical advice only)
- **Child 12-17 years:** 1-2 tablets or 5-10mL suspension after meals and at bedtime

Notes:

- Gaviscon Infant Sachets licensed for infants and young children up to 2 years of age but use <1 year only under medical supervision. Gaviscon liquid and tablets 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.
- Gaviscon Infant should not be used with feed thickeners, nor in patients with excessive fluid losses, (e.g. fever, diarrhoea, vomiting).
- Gaviscon Liquid contains 3.1 mmol sodium per 5mL; Gaviscon tablets contain 2.65 mmol sodium and contain aspartame. Gaviscon Infant Sachets contain 0.92 mmol sodium per dose (half dual sachet).
- 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).
- Can be administed via nasogastric tube or gastrostomy. Not appropriate for administration via jejunostomy.

Evidence: [337-339]

Glycerol (glycerin)

Use:

- Constipation.

Dose and routes
By rectum:

- **Neonate of >34 weeks CorGA:** Tip of a glycerol suppository (slice a small chip off a 1 g suppository with a blade)
- **Child 1 month–11 months:** 1 g infant suppository as required
- **Child 1–11 years:** 2 g child suppository as required
- **Child 12–17 years:** 4 g adult suppository as required

Notes:

- Moisten with water before insertion.
- Hygroscopic and lubricant actions. May also be a rectal stimulant.
- Response usually in 20 minutes to 3 hours.
- Associated with NEC in <34-week babies.
- Available as: suppositories (1 g, 2 g, and 4 g).

Evidence: [337, 338, 420] NoRE

Glycopyrronium bromide

Use:

- Control of upper airways secretion and hypersalivation.

Dose and routes
By mouth:

- **Child 1 month-17 years:** Initial dose of 40 micrograms/kg 3–4 times daily. The dose may be increased as necessary to 100 micrograms/kg 3-4 times daily.
  Maximum 2 mg/dose given 3-4 times daily

Subcutaneous / Intravenous injection:

- **Child 1 month-11 years:** Initial dose of 4 micrograms/kg 3 to 4 times daily. The dose may be increased as necessary to 10 micrograms/kg 3-4 times daily,
  Maximum 200 micrograms/dose given 4 times daily
- **Child 12-17 years:** 200 micrograms every 4 hours when required

Continuous subcutaneous / intravenous infusion:

- **Child 1 month-11 years:** Initial dose of 12 micrograms/kg/24 hours. The dose may be increased as necessary to 40 micrograms/kg/24 hours
  (Maximum 1.2 mg/24 hours)
- **Child 12-17 years:** Initial dose of 600 micrograms /24 hours. The dose may be increased as necessary to 1.2 mg/24 hours. Maximum recommended dose is 2.4 mg/24 hours.

Notes:

- Licensed oral solutions (Sialanar®K, Colonis Pharma 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.
- Excessive secretions can cause distress to the child, but more often cause distress to those around him/her.
- Treatment is more effective if started before secretions become too much of a problem.
- Glycopyrronium does not cross the blood brain barrier and therefore has fewer side effects than hyoscine hydrobromide, which is also used for this purpose. Also fewer cardiac side effects.
- Slower onset response than with hyoscine hydrobromide or butylbromide.
- Oral absorption of glycopyrronium is very poor with wide inter-individual variation.
- Adult evidence for use in smooth muscle spasm (e.g. intestine, bladder), inoperable intestinal obstruction, para-neoplastic pyrexia and sweating and hyperhidrosis.
- Administration by CSCI: good compatibility data available for mixing with other commonly used palliative agents.
- Oral solution: 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.
- For administration via an enteral feeding tube, tablets may be dispersed in water immediately prior to administration, or use the oral solution. Flush tube immediately with

10-20 mL water. There is no specific data on jejunal administration of glycopyrronium. Administer using the above method. Monitor for loss of efficacy or increased side-effects.

- Available as: tablets (1 mg, 2 mg), oral solution (200 micrograms/mL as glycopyrronium bromide (various) and 400 micrograms/mL as glycopyrronium bromide (Sialanar®), injection (200 micrograms/mL 1 mL and 3 ml ampoules).

Evidence: [338, 365, 521, 537, 538]

Haloperidol

Use:

- Nausea and vomiting where cause is metabolic, or in difficult to manage cases such as end stage renal failure.
- Restlessness and confusion / terminal agitation.
- Persistent severe aggression in autism or pervasive developmental disorders.
- Intractable hiccups.
- Psychosis (including steroid induced), hallucinations.

Dose and routes
By mouth for *nausea and vomiting*:

- **Child 1 month–11 years:** 10-20 micrograms/dose every 8-12 hours increased as necessary to a maximum of 50-60 micrograms/kg/dose every 8-12 hours
- **Child 12–17 years:** 1.5 mg once daily at night, increased as necessary to 1.5 mg twice a day; maximum 5 mg twice a day.

By mouth for *restlessness and confusion*:

- **Child 1 month–17 years:** 10–20 micrograms/kg every 8–12 hours; maximum 5 mg twice a day.

By mouth for *intractable hiccups:*

- **Child 1 month–11 years:** Initial dose of 50 micrograms/kg/24 hours (initial maximum 3 mg/24 hrs) in divided doses. The dose may be increased as necessary to a maximum of 170 micrograms/kg/24 hours in divided doses
- **Child 12–17 years:** 1.5 mg 3 times daily.

By continuous IV or SC infusion (for any indication):

- **Child 1 month–11 years:** Initial dose of 25 micrograms/kg/24 hours (initial maximum 1.5 mg/24hrs). The dose may be increased as necessary to a maximum of 85 microgram/kg/24 hours
- **Child 12–17 years:** Initial dose of 1.5 mg/24 hours. The dose may be increased as necessary to a suggested maximum of 5 mg/24 hours although higher doses may be used under specialist advice.

Notes:

- D2 receptor antagonist and typical antipsychotic.
- For dosage in psychosis please discuss with child psychiatrist.
- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for IM administration in adults; IV and SC administration off-label (all ages).
- Haloperidol can cause potentially fatal prolongation of the QT interval and Torsades de Pointes, particularly if given IV (off-label route) or at higher than recommended doses. Caution is required if any formulation of haloperidol is given to patients with an underlying predisposition e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT interval. If IV haloperidol is essential, ECG monitoring during drug administration is recommended.

- Side effects vary between age groups, with behavioural problems being common in children.
- Dosages for restlessness and confusion are often higher.
- Adult dosages can exceed 15 mg/24 hours in severe agitation.
- Oral doses are based on an oral bioavailability of ~50% of the parenteral route i.e. oral doses ~2x parenteral.
- Useful as long acting: – once daily dosing is often adequate.
- Oral solutions may be administered via NG tube or gastrostomy without further dilution. Flush tube well following administration. There is no specific data relating to jejunal administration of haloperidol. Administer using the above method. Monitor for increased side-effects or loss of efficacy.
- Available as: tablets (500 micrograms, 1.5 mg, 5 mg, 10 mg), capsules (500 micrograms), oral liquid (200 micrograms/mL, 1 mg/mL, 2 mg/mL), and injection (5 mg/mL).

Evidence: [337, 338, 340, 341, 345, 471, 539-548]

Hydromorphone

Use:

- Alternative opioid analgesic for severe pain especially if intolerant to other strong opioids.
- Antitussive.

Dose and routes

Normally convert using oral morphine equivalent (OME) from previous analgesia.

Use the following **starting** doses in opioid naive patient. The maximum dose stated applies to **starting** dose only.

By mouth:

- **Child 1–17 years:** 30 micrograms/ kg per dosemaximum 2 mg per dose every 3-4 hours increasing as required. Modified release capsules with an initial dose of 4 mg every 12 hours may be used from 12 years of age.

By IV or SC injection:

- **Child 1-17 years**: Initially 12 micrograms/kg per dose, slowly over at least 2-3 minutes every 3-6 hours.

Notes:

- Hydromorphone injection is licensed for the relief of severe pain in cancer in adults and adolescents aged >12 years. It can be administered by intravenous or subcutaneous injection or infusion.
- Oral form licensed for use in children from 12 years of age with cancer pain.
- Oral bioavailability 37-62% (wide inter-individual variation).
- 1mg of IV hydromorphone is equivalent to 2.5mg of oral hydromorphone.
- Onset of action 15 min for SC, 30 min for oral. Peak plasma concentration 1hour orally.
- Plasma half life 2.5 hours early phase, with a prolonged late phase. Duration of action 4-5 hours.
- Potency ratios seem to vary more than for other opioids. This may be due to inter-individual variation in metabolism or bioavailability.
- An osmotic-release oral delivery system (OROS®) for once daily administration has been developed, but as yet is unauthorized in the UK and Ireland.
- Conversion of oral morphine to oral hydromorphone: divide morphine dose by 7.5
- Conversion of IV morphine to IV hydromorphone: divide morphine dose by 7.5
- Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours, gradually increasing the time interval between doses. After long-term therapy, the dose should be reduced by not more than 10–20% per week.
- Caution in hepatic impairment, use at reduced starting doses.
- Modified release capsules are given 12 hourly.
- Capsules (both types) can be opened and contents sprinkled on soft food. Capsule contents must not however be administered via an enteral feeding tube as likely to cause blockage.
- Available as: capsules (1.3 mg, 2.6 mg) and modified release capsules (2 mg, 4 mg, 8 mg, 16 mg, 24 mg). Injection (2 mg/mL, 10 mg/mL, 20 mg/mL and 50 mg/mL). Oral solution available as a manufacturer's special.

Evidence: [235, 280, 337, 338, 340, 396, 490, 491, 549-554] No RE, ARE

Hyoscine butylbromide

Use:

- Adjuvant where pain is caused by spasm of the gastrointestinal or genitourinary tract (smooth muscle spasm)
- 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 routes
By mouthor IM or IV injection:

- **Child 1 month-4 years:** 300–500 micrograms/kg (maximum 5 mg/dose) 3–4 times daily
- **Child 5-11 years:** 5-10 mg 3–4 times daily
- **Child 12-17 years:** 10–20 mg 3–4 times daily

By continuous subcutaneous infusion:

- **Child 1 month-4 years:** 1.5 mg/kg/24 hours (max 15 mg/24 hours)
- **Child 5-11 years:** 30 mg/24 hours
- **Child 12-17 years:** Up to 60-80 mg/24 hours
- Higher doses may be needed; doses used in adults range from 20-120 mg/24 hours (maximum dose 300 mg/24 hours).

Notes:

- Does not cross blood brain barrier (unlike hyoscine hydrobromide), hence no central antiemetic effect and doesn't cause drowsiness.
- Increased risk of cardiac arrhythmiaand anaphylaxis in patients with underlying cardiac disease.
- Hyoscine butylbromide injection is contraindicated in patients with tachycardia and should be used with caution in patients with cardiac disease. The MHRA recommends that these patients are monitored and that resuscitation equipment and trained personnel are readily available.
- Onset of action <10 min for SC/IV; 1–2 hours for PO. Time to peak plasma concentration 15 min–2 hours PO. Plasma half-life 1–5 hours. Duration of action <2 hours in adult volunteers but possibly longer in moribund patients.
- Oral bioavailability, based on urinary excretion, is <1%. Thus, any antispasmodic effect reported after PO administration probably relates to a local contact effect on the GI mucosa.
- Likely to exacerbate acid reflux.
- Tablets are not licensed for use in children <6 years old.
- Injection is not licensed for use in children.
- The injection solution may be given orally or via an enteral feeding tube. If the tube exits in the jejunum, consider using parenteral therapy. Injection solution can be stored for 24hours in the refrigerator.
- IV injection should be given slowly over 1minute and can be diluted with glucose 5% or sodium chloride 0.9%.
- Available as: tablets (10 mg) and injection (20 mg/mL).

Evidence: [337, 338, 345, 365, 538, 555-560]

Hyoscine hydrobromide

Use:

- Control of upper airways secretions and hypersalivation
- Bowel colic pain
- Paraneoplastic sweating or pyrexia

Dose and routes
By mouth or sublingual:

- **Child 2–11 years:** 10 micrograms/kg (maximum 300 micrograms single dose) 4 times daily
- **Child 12–17 years:** 300 micrograms 4 times daily

By transdermal route:

- **Neonate >32weeks CorGA - Child 2 years:** Quarter of a patch every every72 hours
- **Child 3–9 years:** Half of a patch every 72 hours
- **Child 10–17 years:** One patch every 72 hours

By SC or IV injection or infusion:

- **Child 1 month–17 years:** 10 micrograms/kg (maximum 600 micrograms) every 4–8 hours or CSCI/IV infusion 40-60 micrograms/kg/24 hours. Maximum suggested dose is 2.4 mg in 24 hours although higher doses are often used by specialist units.

Notes:

- Not licensed for use in children for control of upper airways secretion and hypersalivation.
- Higher doses often used under specialist advice.
- Can cause delirium or sedation (sometimes paradoxical stimulation) with repeated dosing.
- Constipating. May exacerbate acid reflux.
- Apply patch to hairless area of skin behind ear.
- The patch can cause alteration of the pupil size on the side it is placed.
- Transdermal patches contain metal in the backing and must be removed before MRI scanning to avoid burns.
- Some specialists advise that transdermal patches should not be cut – however, the manufacturers of Scopoderm TTS patch have confirmed that it is safe to do this although outside of the product licence.
- Injection solution may be administered orally.
- Available as: tablets (150 micrograms, 300 micrograms),
  patches (releasing 1 mg/72 hours), and
  injection (400 microgram/mL, 600 microgram/mL).
  An oral solution is available via a ‘specials’ manufacturer.

Evidence: [337, 338, 365, 420, 537, 538, 558]

Ibuprofen

Use:

- Simple analgesic
- Pyrexia
- Adjuvant for musculoskeletal pain.

Dose and routes
By mouth:

- **Neonate:** 5 mg/kg/dose every 12 hours
- **Child 1–2 months:** 5 mg/kg 3–4 times daily preferably after food
- **Child 3–5 months:** 50 mg 3 times daily preferably after food; in severe conditions up to 30mg/kg daily in 3–4 divided doses
- **Child 6 months–11 months:** 50 mg 3–4 times daily preferably after food; in severe conditions up to 30 mg/kg daily in 3–4 divided doses
- **Child 1-3 years:** 100 mg 3 times daily preferably after food. In severe conditions up to 30 mg/kg daily in 3–4 divided doses
- **Child 4–6 years:** 150 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses
- **Child 7–9 years:** 200 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4 g
- **Child 10–11 years:** 300 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses. Maximum daily dose 2.4 g
- **Child 12-17 years:** 300-400 mg 3-4 times daily preferably after food. In severe conditions the dose may be increased to a maximum of 2.4 g/day

Pain and Inflammation (by mouth using modified release preparation)

- **For Child 12–17 years:** 1.6 g once daily, dose preferably taken in the early evening, increased to 2.4 g daily in 2 divided doses, dose to be increased only in severe cases.

Pain and inflammation in rheumatic diseases, including idiopathic juvenile arthritis:

- **Child aged 3 months–8 years and body weight > 5kg**: 30–40 mg/kg daily in 3–4 divided doses preferably after food. Maximum 2.4 g daily.

In systemic juvenile idiopathic arthritis:

- Up to 60 mg/kg daily in 4–6 divided doses up to a maximum of 2.4 g daily (off-label).

Notes:

- **Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease.**
- Orphan drug licence for closure of ductus arteriosus in preterm neonate.
- Not licensed for use in children less than 3 months of age or 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.
- Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.
- Ibuprofen is a non-opioid analgesic, NSAID and non-selective COX inhibitor.

- Its analgesic effect can be as potent as low dose morphine.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk).
- Caution in asthma and during chemotherapy and look out for symptoms and signs of gastritis.
- Consider use of a proton pump inhibitor with prolonged use of ibuprofen.
- For administration via an enteral feeding tube, use a liquid preparation; dilute with an equal volume of water immediately prior to administration where possible. No specific information for jejunal administration. Administer as above and monitor for any signs of loss of efficacy or increased side-effects.
- Ibuprofen can be used topically particularly for sprains, strains and arthritis.
- Available as: tablets (200 mg, 400 mg, 600 mg), modified release tablet (800 mg), orodispersible tablets (200 mg), chewable capsules (100 mg), capsules (200 mg, 400 mg), modified release capsules (200 mg, 300 mg), oral syrup (100 mg/5 mL), granules (600 mg/sachet), and spray, foam (50 mg per 1 g) creams and gels (5%).

Evidence: [337-339, 345, 561-565]

Ipratropium Bromide

Use:

- Wheezing/ Breathlessness caused by bronchospasm
- Localised management of sialorrhoea (with less systemic side effects)
- Rhinorrhoea associated with allergic and non-allergic rhinitis

Dose and routes:
Nebulised solution

- **Child 1 month-5 years:** 125-250 micrograms as required maximum 1 mg per day
- **Child 6-11 years:** 250 micrograms as required maximum 1 mg per day
- **Child 12-17 years:** 500 micrograms as required maximum 2 mg per day

Aerosol inhalation

- **Child 1 month-5 years:** 20 micrograms 3 times daily
- **Child 6-11 years:** 20-40 micrograms 3 times daily
- **Child 12-17 years:** 20-40 micrograms 3-4 times daily

Rhinorrhoea associated with allergic and non-allergic rhinitis
By intranasal administration

- **Child 12–17 years:** 2 sprays 2–3 times a day, dose to be sprayed into each nostril.

Notes

- Inhaled product should be used with a suitable spacer device, and the child/carer should be given appropriate training.
- In acute asthma, use via an oxygen driven nebuliser.
- Maximum effects 30-60 minutes after use.
- Duration of action 3-6 hours.
- Bronchodilation can usually be maintained with treatment 3 times a day.
- In severe acute asthma, dose can be repeated every 20-30 minutes in first two hours, then every 4-6 hours as necessary.
- Anti-muscarinic side effects occur with systemic absorption, including constipation, urinary retention, tachycardia, blurred vision.
- Available as: nebuliser solution (250 micrograms in 1 mL, 500 micrograms in 2 mL), aerosol inhaler (20 microgram per metered dose), nasal spray 21 microgram per metered dose.

Evidence: [338, 341, 566, 567] SRE

Ketamine

Use:

- Adjuvant to a strong opioid for neuropathic pain.
- Severe visceral pain / visceral hyeralgesia[340].
- Ischaemic pain.
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance.
- Emerging use in refractory status epilepticus.
- In neonates: for induction and maintenance of anaesthesia during procedures.
- Psychiatric use for treatment resistant depression in adolescents (secondary effect that this may offer, rather than because we advocate starting drugs for psychiatric diagnoses).

Dose and routes
By mouth or buccal or sublingual:

- **Neonate (>37 weeks CorGA) – Child 11 years:** Starting dose 100 microgram/kg, as required or regularly 6–8 hourly: increasein increments of 100 microgram/kg up to 400 microgram/kg as required. Doses equivalent to 3 mg/kg have been reported in adults
- **Over 12 years and adult:** 5-10 mg as required or regularly 6–8 hourly; increase in steps of 5-10 mg up to 50 mg as required. Doses up to 200 mg 4 times daily reported in adults

By continuous SC or IV infusion:

- **Child 1 month–adult:** Starting dose 20-40 micrograms/kg/hour. Increase according to response; usual maximum 100 micrograms/kg/hour. Doses up to 1.5 mg/kg/hour in children and 2.5 mg/kg/hour in adults have been reported.

By intravenous administration*for anaesthesia*.

- **Neonates:**
  - **Short procedures**: 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response. By intravenous injection over at least 60 seconds
  - **Longer procedures**: Initially 0.5–2 mg/kg by intravenous injection, followed by a continuous intravenous infusion of 8micrograms/kg/minute adjusted according to response; up to 30 micrograms/kg/minute may be used to produce deep anaesthesia

Notes:

- NMDA antagonist.
- Specialists use only.
- Not licensed for use in children with neuropathic pain.
- Ketamine is a racemic mixture: The S(+) and R(–) stereoisomers of ketamine bind to the dizocilpine site of the NMDA receptor with different affinities, the former showing approximately 2-to-3-fold greater affinity for the receptor than the latter.
- In many countries s-ketamine is licensed. For s-ketamine usually you divide the ketamine dose by 2.
- Higher doses (bolus injection 1–2 mg/kg, infusions 0.6-2.7 mg/kg/hour) used as an anaesthetic e.g. for short procedures.
- Sublingual doses should be prepared in a maximum volume of 2 mL. The bitter taste may make this route unpalatable. Special preparations for sublingual use are available in UK.

- Enteral dose equivalents may be as high as 3 times the IV or SC dose because ketamine is potentiated by hepatic first pass metabolism. Some papers quote a 1:1 SC to oral conversion ratio and other1:6 IV to oral conversion.
- Agitation, hallucinations, anxiety, dysphoria, diplopia, nystagmus, vomiting and sleep disturbance are recognised side effects. These may be less common in children and when sub-anaesthetic doses are used.
- Ketamine can cause urinary tract symptoms- frequency, urgency, dysuria and haematuria. Consider discontinuing ketamine if these symptoms occur.
- Caution in severe hepatic impairment, consider dose reduction.
- In view of ketamine's side-effect profile including cognitive impairment and renal tract damage, long-term use should be avoided if possible.
- Do not stop suddenly as hyperalgesia or allodynia may occur. Withdraw over 2-3 weeks.
- Animal studies indicate that it can induce neuronal cell death in the immature brain. No real preterm outcome data, so only for use in babies over 37weeks CorGA.
- Dilute in 0.9% saline for subcutaneous or intravenous infusion.
- Can be administered as a separate infusion or by adding to opioid infusion/ PCA/NCA.
- Can also be used intranasally and as a topical gel.
- Intranasal esketamine is licensed in the USA to treat refractory depression.
- Oral solution may be administered via an enteral feeding tube. No specific information on jejunal administration.
- Available as: Injection (10 mg/mL, 50 mg/mL, 100 mg/mL) and oral solution 50 mg in 5 mL (from a 'specials' manufacturer). Injection solution may be given orally. Mix with a flavoured soft drink to mask the bitter taste. Schedule 2 CD.

Evidence: [251, 338, 491, 552, 568-586] WRE, ARE

Ketorolac

Use:

- Short-term management of moderate to severe acute postoperative pain; limited evidence of extended use in chronic pain.

Doses and routes:

Short-term management of moderate to severe acute postoperative pain (NB Licensed duration is a maximum of 2 days; not licensed for use in adolescents and children less than 16 years of age).

IV bolus (over at least 15 seconds) or IM bolus:

- **Child 1-15years:** Initially 0.5–1 mg/kg (max. 10mg), then 500 micrograms/kg (max. 15 mg) every 6 hours as required; max. 60 mg daily
- **Child >16 years:** Initially 10mg, then 10–30 mg every 4–6 hours as required (up to every 2 hours during initial postoperative period); max. 90 mg daily (those weighing less than 50 kg max. 60 mg daily).

Chronic pain in palliative care (unlicensed indication; data limited and of poor quality. Anecdotal reports of effectiveness for patients with bone pain unresponsive to oral NSAIDs).

Sublingual

- **Child 4-18 years:** 0.5 mg/kg up to three times a day (usinginjection solution)

SC bolus

- **Child>16 years:** 15-30 mg/dose, three times daily

CSCI

- **Child >16 years:** Initial dose of 60 mg/24 hours.
  Increase, if necessary, by 15 mg/24 hours to a maximum of 90 mg/24 hours

Notes:

- Ketorolac is a non-opioid, NSAID and preferential COX-1 inhibitor which has potent analgesic effects with only moderate anti-inflammatory action.
- Licensed only for the short-term management (maximum of 2 days) of moderate to severe acute postoperative pain in adults and adolescents from 16 years of age.
- SC administration is an unlicensed route of administration.
- Contraindications: previous hypersensitivity to ketorolac or other NSAIDs; history of asthma; active peptic ulcer or history of GI bleeding; severe heart, hepatic or renal failure; suspected or confirmed cerebrovascular bleeding or coagulation disorders. Do not use in combination with any other NSAID.
- Dose in adults with mild renal impairment should not exceed 60mg/day.
- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates ketorolac and piroxicam are associated with the highest risk. Use the lowest effective dose for the shortest time. In addition, consider use in combination with a gastro-protective drug especially if ketorolac is used for a prolonged period (outside the licensed indication). Use of ketorolac in adults carries a 15 times increased risk of upper

gastrointestinal complications, and a 3 times increased risk compared with other nonselective NSAIDs.

- In adults all NSAID use can, to varying degrees, be associated with a small increased risk of thrombotic effects. The risk of cardiovascular effects secondary to NSAID use is undetermined in children, but in adults, ketorolac is associated with the highest myocardial infarction risk of all NSAIDs.
- Other potential adverse effects;
  - Very common (>10% patients): headache, dyspepsia, nausea, abdominal pain.
  - Common (1-10% patients): dizziness, tinnitus, oedema, hypertension, anaemia, stomatitis, abnormal renal function, pruritus, purpura, rash, bleeding and pain at injection site. Risk of adverse effects likely to increase with prolonged use.
- Drug interactions include anticoagulants (contraindicated as the combination may cause an enhanced anticoagulant effect); corticosteroids (increased risk of GI ulceration of bleeding); diuretics (risk of reduced diuretic effect and increase the risk of nephrotoxicity of NSAIDs); other potential nephrotoxic drugs.
- Onset of action 10-30mins when IV/IM; maximal analgesia achieved within 1-2 hours and median duration of effect 4-6 hours.
- Potent NSAID equivalent to twice the strength of naproxen.
- SC injection can be irritant therefore dilute to the largest volume possible (0.9% NaCl suggested). Alkaline in solution so high risk of incompatibility if mixed with acidic drugs. Some data of compatibility in 0.9% sodium chloride with diamorphine or oxycodone. Incompatibilities include with cyclizine, glycopyrronium, haloperidol, levomepromazine, midazolam and morphine.
- Available as: Injection 30 mg/mL (injection contains ethanol as an excipient) and eye drops (5 mg per 1mL) for use in inflammation after eye surgery.
- Oral 10 mg tablets and injection 10 mg/mL no longer available in the UK (discontinued early 2013 due to lack of demand).

Evidence: [337, 552, 587-599]

Lactulose

Use:

- Constipation, faecal incontinence related to constipation.
- Hepatic encephalopathy (portal systemic encephalopathy) and coma.

Dose:

Constipation:

By mouth: initial dose twice daily then adjusted to suit patient

- **Neonate:** 2.5 mL/dose twice a day
- **Child 1 month-11 months:** 2.5 mL/dose 1-3 times daily
- **Child 1year-4 years:** 5 mL/dose 1-3 times daily
- **Child 5-9 years:** 10 mL/dose 1-3 times daily
- **Child 10-17 years:** 15 mL/dose 1-3 times daily.

Hepatic encephalopathy:

- **Child 12-17 years:** use 30-50mL three times daily as initial dose. Adjust dose to produce 2-3 soft stools per day.

Notes:

- Licensed for constipation in all age groups. Not licensed for hepatic encephalopathy in children.
- Increases colonic bacterial flora (macrogols do not).
- Side effects may cause nausea and flatus, with colic especially at high doses. Initial flatulence usually settles after a few days.
- Precautions and contraindications; Galactosaemia, intestinal obstruction. Caution in lactose intolerance.
- Use is limited as macrogols are often better in palliative care. However the volume per dose of macrogols is 5-10 times greater than lactulose and may not be tolerated in some patients.
- Lactulose is less effective than macrogols, or sodium picosulfate for opioid induced constipation in ambulatory palliative care patients.
- Sickly taste.
- Onset of action can take 36-48 hours.
- May be taken with water and other drinks.
- May be administered via NG tube or gastrostomy. Dilution with 2-3x the volume of water will reduce the viscosity of the solution and aid administration. As the site of action is the colon, lactulose will have a therapeutic effect if it is delivered directly into the stomach or jejunum. Administer using the above method.
- 15 mL/day is 14 kcal so unlikely to affect diabetic or ketogenic diets.
- Does not irritate or directly interfere with gut mucosa.
- Available as oral solution 10 g/15 mL or 680 mg/1 mL. Cheaper than Movicol (macrogol).

Evidence: [25, 337, 338, 340, 341, 420, 600-603]

Lansoprazole

Uses:

- 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:
Oral

- **Child body weight <30 kg:** 0.5-1 mg/kg with maximum 15 mg once daily in the morning
- **Child body weight>30 kg:** 15-30 mg once daily in the morning

Notes:

- Lansoprazole is not licensed in the UK for infants, children or adolescents. Lansoprazole is however licensed in the US for use from 1 year of age. Exact doses limited by available formulations.
- Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H+/K+ ATPase of the parietal cells in the stomach. The inhibition is dose dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid.
- For optimal effect, the single daily dose is best taken in the morning.
- Lansoprazole should be taken at least 30 minutes before food, as intake with food slows down the absorption and decreases the bioavailability.
- The dose may be increased if symptoms do not fully resolve (consider increasing the single daily dose or BD dosing).
- Studies in infants and children indicate they appear to need a higher mg/kg dose than adults to achieve therapeutic acid suppression.
- Oral bioavailability is good at 80-90% compared to 60% for omeprazole.
- There is some anecdotal experience that Lansoprazole FasTabs may be halved to give a 7.5 mg dose.
- No dose adjustment is needed in patients with renal impairment. Reduction of dose (50%) is recommended in patients with moderate to severe hepatic impairment.
- Hypomagnesaemia may develop with prolonged use.
- Common adverse effects (>1 in 100 to <1 in 10): headache, dizziness; nausea, diarrhoea, stomach pain, constipation, vomiting, flatulence, dry mouth, pharyngitis, increase in liver enzyme levels, urticaria, itching, rash.
- Lansoprazole may interfere with absorption of drugs where gastric pH is critical to its bioavailability (e.g. atazanavir, itraconazole); may cause increase in digoxin levels and increase in plasma concentration of drugs metabolised by CYP3A4 (e.g. theophylline and tacrolimus). Drugs which inhibit or induce CYP2C19 or CYP3A4 may affect the plasma concentration of lansoprazole. Sucralfate and antacids may decrease the bioavailability of lansoprazole.
- PPIs are an independant risk factor for Clostridium Difficile infection.
- MHRA safety warning 2015: there is a very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs.
- Capsules: Capsules should be swallowed whole with liquid. For patients with difficulty swallowing, studies and clinical practice suggest that the capsules may be opened and the

granules mixed with a small amount of water, apple/tomato juice or sprinkled onto a small amount of soft food (e.g. yoghurt, apple puree) to ease administration.

- FasTabs: Place on the tongue and gently suck. The FasTab rapidly disperses in the mouth releasing gastro-resistant microgranules which are then swallowed. FasTabs can be swallowed whole with water or mixed with a small amount of water if preferred. FasTabs contain lactose and aspartame and should be used with caution in known PKU patients.
- For administration via a NG or gastrostomy tube, lansoprazole FasTabs can be dispersed in 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. Lansoprazole is absorbed in the small bowel; therefore, jejunal administration is not expected to reduce bioavailability. Administer as above.
- Available as 15 mg and 30 mg capsules and 15 mg and 30 mg orodispersible tablets.

Evidence: [96, 337, 338, 340, 345, 604-617]

Levetiracetam

Use:

- Epileptic seizures

Dose and route:

Background seizure management

By mouth.

- **Child 1-5 months:** Initially 7 mg/kg once daily then increase in steps of up to 7 mg/kg twice daily (maximum per dose 21 mg/kg twice daily). Dose to be increased every 2 weeks
- **Child 6 months–17 years (body weight up to 50 kg):** Initially 10 mg/kg once daily, then increase in steps of up to 10 mg/kg twice daily (maximum per dose 30 mg/kg twice daily). Dose to be increased every 2 weeks
- **18 years and over or body weight 50 kg and above:** 250 mg twice daily then increase in steps of 500 mg twice daily (maximum per dose 1.5 g twice daily). Dose to be increased every 2-4 weeks

By intravenous route

- **Body weight up to 50 kg:**10 mg/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
- **Body weight 50 kg and above:** 250 mg twice daily then increase in steps of 500 mg twice daily (maximum per dose 1.5 g twice daily). Dose to be increased every 2-4 weeks

By Continuous Subcutaneous or Intravenous Infusion.

- **Dose conversion for oral:intravenous:subcutaneous is 1:1:1**
- **Take total daily oral or intravenous dose and give as subcutaneous or intravenous infusion over 24hours**

Management of breakthrough seizures

Can be used for breakthrough seizure management in prolonged seizures, usually after other first line medications have been tried (e.g. midazolam, paraldehyde).

No need to measure levels

By enteral, subcutaneous or intravenous route

- **Neonate:** 10-20 mg/kg, then top up after 2-12 hours if required, with 10–20mg/kg, aiming not to give more than 40mg/kg/day (including any routine dose in this calculation)
- **Child over 1 month:** 20 mg/kg then top up after 2-12 hours if required, with 10–20 mg/kg, aiming not to give more than 60 mg/kg/day (including any routine dose in this calculation)

Notes:

- Benefits of levetiracetam over phenobarbitone or phenytoin for breakthrough seizure management include fewer side effects and lower volume enteral dose availability.

- Can be combined in syringe driver with midazolam, morphine, hyoscine butylbromide, hydromorphone, methotrimeprazine, metoclopramide, dexamethasone, haloperidol, glycopyrrolate and clonidine.
- Dilute in 0.9% NaCl. IV doses should be given over at least 15 minutes.
- Dilute to largest volume possible to minimise pain and irritation on administration. Dose for intravenous infusion should be diluted to a suggested concentration of around 15 mg/mL with a compatible diluent and administered as a 15-minute intravenous infusion. For subcutaneous administration need to dilute to a concentration of 15 mg/mL or less as high osmolarity may cause tissue damage. It is therefore preferable to use the intravenous or enteral route.
- Can be given as twice daily bolus subcutaneously subject to volume consideration.
- Available as: Tablets 250 mg, 500 mg, 750 mg and 1 g; Oral solution 100 mg/mL; Solution for Infusion 100 mg/mL.

Evidence: [337, 338, 618-621] NoRE

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

Dose and routes
Used as antiemetic
By mouth:

- **Child 2–11 years:** Initial dose 50-100 micrograms/kg given once or twice daily. This dose may be increased as necessary and as tolerated. Not to exceed 1mg/kg/dose (or maximum of 25 mg/dose) given once or twice daily
- **Child 12-17 years:** Initial dose 3 mg once or twice daily. This dose may be increased as necessary and as tolerated to a maximum of 25 mg once or twice daily.

By continuous IV or SC infusion over 24hours:

- **Child 1 month–11 years:** Initial dose of 100micrograms/kg/24 hours increasing as necessary to a maximum of 400micrograms/kg/24 hours. Maximum 25mg/24 hours
- **Child 12–17 years:** Initial dose of 5 mg/24 hours increasing as necessary to a maximum of 25 mg/24 hours

By SC or IV injection:

- **Child 12–17 years:** Initial as required dose 2.5 mg given once or twice daily.

Used for sedation and confusion
By continuous subcutaneous or intravenous infusion over 24hours:

- **Child 1 year–11 years:** Initial dose of 350 micrograms/kg/24 hours (maximum initial dose 12.5 mg), increasing as necessary up to 3 mg/kg/24 hours
- **Child 12–17 years:** Initial dose of 12.5mg/24 hours increasing as necessary up to 200 mg/24 hours.

By SC or IV injection:

Child 12–17 years: Initial dose of
Child <35 kg as required dose 2.5 mg given once or twice daily.
Child >35 kg as required dose 5 mg given once or twice daily.

Notes:

- Licensed for use in children with terminal illness for the relief of pain and accompanying anxiety and distress.
- A low dose is often effective as antiemetic. Titrate up as necessary. Higher doses are very sedative and this may limit dose increases.
- If the child is not stable on high dosage for nausea and vomiting, reconsider cause and combine with other agents e.g. dexamethasone.
- Some experience in adults withbuccal use at low dose as antiemetic (e.g. 1.5 mg three times daily as needed).

- Can cause hypotension, particularly with higher doses. Somnolence and asthenia are frequent side effects.
- Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of cytochrome P450 2D6. Co-administration of levomepromazine and drugs primarily metabolised by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of these drugs.
- May lower seizure threshold.
- Avoid, or use with caution, in patients with liver dysfunction or cardiac disease. Start at low dose in patients with severe renal impairment and give once daily, titrating according to response.
- 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. There is no specific information relating to jejunal administration of levomepromazine. Administer using the above method. Monitor for loss of efficacy or increased side-effects.
- For SC infusion dilute with sodium chloride 0.9%. Water for injection may also be used. The SC dose is considered to be twice as potent as that administered orally.
- Available as: tablets (25 mg) and injection (25 mg/mL). A 6 mg tablet is also available via specialist importation companies. An extemporaneous oral solution may be prepared.

Evidence: [209, 297, 337, 338, 340, 345, 622, 623] CC, EA

Lidocaine (Lignocaine) patch

Use

- Localised neuropathic pain

Dose and routes
Topical:

- **Child 3–17 years:** Apply 1-2 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period (to help reduce risk of skin reactions)
- **Adult 18 years or above:** Up to 3 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period (to help reduce the risk of skin reactions).

Notes:

- Not licensed for use in children or adolescents under 18 years.
- The lidocaine in the plaster diffuses continuously into the skin, providing a local analgesic effect. The mechanism by which this occurs is through stabilisation of neuronal membranes, thought to cause down-regulation of sodium channels resulting in pain reduction.
- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes.
- When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 hours) about 3± 2% of the total applied lidocaine dose is systemically available and is similar for single and multiple administrations.
- Maximum recommended number of patches in adults currently is 3 per application.
- The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product.
- The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
- 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.
- The plasters must be used within 14 days of opening the sachets.
- A recent analysis by anatomic site of patch placement suggests that application to the head was tolerated less well compared with the trunk and extremities.
- Doses extrapolated from BNF online Aug 2019.
- Available as 700 mg/medicated plaster (5% w/v lidocaine).

Evidence: [337, 340, 624-631] NoRE, ARE

Lomotil® (co-phenotrope)

Use:

- Diarrhoea from non-infectious cause.
- Control of faecal consistency after colostomy or ileostomy.

Dose and routes
Tablets: diphenoxylate hydrochloride 2.5mg, atropine 25micrograms

By mouth:

- **Child 2–3 years:** Half tablet 3 times daily
- **Child 4–8 years:** 1 tablet 3 times daily
- **Child 9–11 years:** 1 tablet 4 times daily
- **Child 12–15 years:** 2 tablets 3 times daily
- **Child 16–17 years:** Initially 4 tablets then 2 tablets 4 times daily.

Notes:

- A mixture of diphenoxylate hydrochloride and atropine sulfate in proportions of 100:1.
- Not licensed for use in children < 4 years.
- Tablets may be crushed. For administration via a NG tube or gastrostomy, tablets may be crushed and dispersed in water immediately before use. There is no specific information on jejunal administration – suggest administered as above.
- Young children are particularly susceptible to overdosage, which is primarily an opioid intoxication (central nervous system and respiratory depression with miosis), occasionally associated with atropine toxicity (central nervous system excitement, hypertension, fever, flushed dry skin). Atropine effects occur before, during, or after opioid effects. Symptoms may be delayed and observation is needed for at least 48 hours after ingestion. Overdose can be difficult to manage with a mixed picture of opioid and atropine poisoning. Furthermore, the presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals.
- Available only as tablets Co-Phenotrope (2.5 mg diphenoxylate hydrochloride and
- 25 micrograms atropine sulphate).

Evidence: [337, 338, 632-635]

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:** Initial dose of 100 micrograms/kg twice daily given 30 minutes before feeds. Increase as necessary up to a maximum of 2 mg/kg/day given in divided doses
- **Child 1–11years:** Initial dose of 100 micrograms/kg (maximum single dose 2 mg) 3-4 times daily. Increase as necessary up to a maximum of 1.25 mg/kg/day given in divided doses (maximum 16 mg/day)
- **Child 12–17years:** Initial dose of 2 mg 2-4 times daily. Increase as necessary up to a maximum of 16 mg/day given in divided doses.

Notes:

- Not licensed for use in children with chronic diarrhoea.
- Capsules not licensed for use in children < 8 years.
- Syrup not licensed for use in children < 4 years.
- Common side effects: constipation, nausea, flatulence.
- As an antidiarrhoeal, loperamide is about 50x more potent than codeine. It is longer acting; maximum therapeutic impact may not be seen for 16-24 hours.
- For NG or gastrostomy administration: Use the liquid preparation undiluted. Flush well after dosing. Alternatively, the tablets can be used without risk of blockage, although efficacy is unknown. Jejunal administration will not affect the therapeutic response to loperamide. However, owing to the potential osmotic effect of the liquid preparation, it may be appropriate to further dilute the dose with water immediately prior to administration.
- Available as tablets (2 mg), capsules (2 mg), orodispersible tablets (2 mg) and oral syrup (1 mg/5 mL).

Evidence: [337, 338, 345, 636-638]

Lorazepam

Use

- Background anxiety.
- Agitation and distress.
- Adjuvant in cerebral irritation.
- Background management of dyspnoea.
- Muscle spasm.
- Status epilepticus.

Dose and routes for all indications except status epilepticus:
By mouth:

- **Child < 2 years:** 25 micrograms/kg 2–3 times daily
- **Child 2–5 years:** 500 micrograms 2–3 times daily
- **Child 6–10 years:** 750 micrograms 3 times daily
- **Child 11–14 years:** 1 mg 3 times daily
- **Child 15–18 years:** 1–2 mg 3 times daily.

Sublingual:

- **Children of all ages**: 25 micrograms/kg as a single dose. Increase to 50 micrograms/kg (maximum 1 mg/dose) if necessary
- **Usual adult dose**: 500 micrograms–1mg as a single dose, repeat as required.

For status epilepticus
By Slow IV injection:

- **Neonate:** 100 micrograms/kg for a single dose then 100microgram/kg after 10 minutes if required
- **Child 1 month–11 years:** As above with a maximum single dose of 4mg
- **Child 12-17years:** 4 mg for a single dose then a further 4 mg after 10 minutes if required.

Notes

- Not licensed for use in children for these indications other than status epilepticus.
- Tablets licensed in children over 5 years for premedication, injection not licensed in children less than 12 years except for treatment of status epilepticus.
- Potency in the order of 10 times that of diazepam per mg as anxiolytic/sedative.
- Well absorbed sublingually with rapid onset of effect. There may however be variable absorption by this route with further variation possible depending on the formulation used.
- Specific sublingual 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 sublingually.
- Tablets may be dispersed in water for administration via an enteral feeding tube. There is no specific information on jejunal administration. Monitor for increased side-effects or loss of efficacy.
- May cause drowsiness and respiratory depression if given in large doses.
- Caution in renal and hepatic failure.
- Available as tablets (1 mg, 2.5 mg) and injection (2 mg/mL and 4 mg/mL).

Evidence: [338, 340, 345, 540, 639] NoRE, ARE

Macrogols

Use

- Constipation.
- Faecal impaction.
- Suitable for opioid-induced constipation.

Dose and routes paediatric sachets for those less than 12 years of age);

By mouth for constipation or prevention of faecal impaction:

- **Child under 1 year:** ½-1 paediatric sachet daily
- **Child 1–5 years:** 1 paediatric sachet daily (adjust dose according to response; maximum 4 sachets daily)
- **Child 6–11 years:** 2 paediatric sachets daily (adjust dose according to response; maximum 4 sachets daily)
- **Child 12–17 years:** 1–3 **adult**sachets daily.

By mouth for faecal impaction:

- **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
- **Child 12–17 years:** 4 sachets daily of **adult** preparation, then increase by 2 sachets daily to a maximum of 8 adult sachets daily. Total daily dose should be drunk within a 6 hour period. After disimpaction switch to maintenance laxative therapy.

Notes

- Not licensed for use in children < 5 years with faecal impaction and < 2 years with chronic constipation.
- Need to maintain hydration. Caution if fluid or electrolyte disturbance.
- Caution with high doses (volumes) in those with impaired gag reflex, reflux oesophagitis or impaired consciousness.
- Do not use adult sachets in children. Risk of electrolyte imbalance.
- Mix powder with water: follow manufacturers' instructions.
- For administration via a feeding tube: dissolve the powder (or liquid concentrate) in water as directed and flush down the feeding tube. Flush well after dosing. As the mechanism of action is local within the bowel, jejunal administration should not affect efficacy. Administer as above.
- Macrogol oral powder is available as Movicol and Movicol Paediatric Sachets, CosmoColand CosmoCol Paediatric Sachets, Laxido and Laxido Paediatric Sachets, Macilax and Macilax Paediatric Sachets. Movicol is also available as a liquid concentrate (dilute with water before administration).

Evidence: [25, 34, 337, 338, 345, 640]

Melatonin

Use:

- Sleep disturbance due to disruption of circadian rhythm (*not* anxiolytic).

Dose and routes
By mouth:

- **Child 1 month-17 years:** Initial dose 2–3 mg, increasing every 1–2 weeks dependent on effectiveness up to maximum 10mg daily.

Notes:

- 1 mg and 5 mg m/r tablets (Slenyto®) licensed in children for insomnia with ASD and Smith-Magenis syndrome. All other formulations of melatonin are not licensed for use in children or are unlicensed 'special' formulations.
- Specialists use only.
- Reduced clearance in hepatic impairment.
- Some prescribers use a combination of immediate release and m/r tablets to optimise sleep patterns.
- Immediate release capsules may be opened and the contents sprinkled on cold food if preferred. If available, sustained release capsules may also be opened but the contents should not be chewed. If administration via an enteral feeding tube is required, use of an unlicensed liquid special is preferred.
- Licensed UK formulations: 1 mg and 5 mg m/r tablets (Slenyto®) and 2 mg m/r tablets (Circadin®) and 1 mg/mL oral solution (Colonis®)). Various unlicensed formulations, including immediate release capsules and oral liquid may be available from 'specials' manufacturers or specialist importing companies.

Evidence: [337, 338, 641-658] NoRE

Methadone

(WARNING: requires specialist advice)
Use:

- Major opioid used for moderate to severe pain, particularly neuropathic pain and pain poorly responsive to other opioids.
- Not normally used as first line analgesia in the UK.

Caution:
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.

Dose and routes

In opioid naïve children
By mouth:

- **Child 1-12 years:** 30-100 micrograms/kg (maximum 5mg/dose initially) 1-3 times daily
- **Child >12 years:**100-200 micrograms/kg every 8-12 hours (maximum 5 mg/dose initially)
- Methadone has a long and variable half-life with potential to cause sedation, respiratory depression and even death from secondary peak phenomenon.
- Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may berequired 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 25% approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently).
- Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.
- For breakthrough pain, we would recommend using a short half-life opioid.

In opioid substitution/ rotation or switch
Caution:

Substitution, rotation or switch to methadone is a specialist skill and should only be undertaken in close collaboration with practitioners experienced in its use. There is a risk of unexpected death through overdose.

- 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 for 5-6 days or titrate orally at home with **very close** supervision.
- Other opioids should be considered first, if switching from morphine due to unacceptable effects or inadequate analgesia.

Consultation with a pain clinic or specialist palliativecare service is advised

Equianalgesic doses:

Dose conversion ratios from other opioids are not static but are a function of previous opioid exposure and are highly variable.

Published tables of equianalgesic doses of opioids, established in healthy non-opioid tolerant individuals, indicate that methadone is 1–2 times as potent as morphine in single dose studies, but in individuals on long-term (and high dose) morphine, methadone is closer to 10 times as potent as morphine; it can be 30 times more potent or occasionally even more. The potency ratio tends to increase as the dose of morphine increases.

Ref [235]

In adults there are several protocols for opioid rotation to methadone which are not evidence based in paediatrics.

- One approach incorporates a transition period where the dose of the former opioid is reduced and partially replaced by methadone which is then titrated upwards [659]. This approach is considered safer.

- In another approach, previous opioid therapy is completely stopped before starting a fixed dose of methadone at variable dose intervals [660]. This approach carries more risks.

<u>To switch smoothly to methadone</u>

Day1: 30% reduction of former opioid and substitute with oral methadone divided in 3 doses

Conversion rate: (Morphine in mg: Methadone in mg)

OME 30-90 mg/day	= 4:1[661]
OME 90-300 mg/day	= 6:1[661]
OME 301-600 mg/day	= 8:1[661]
OME 601-800 mg/day	= 12:1 [662]
OME 801-1000 mg/day	= 15:1[662]

That means; if the OME dose is 900 mg/day; 1/3 is 300 mg/day and the equianalgesic methadone dose is 20 mg, add to the remaining 600 mg OME the 3 x 6.5 mg methadone

Next day reduce according to result of first reduction, i.e., by further 300 mg OME

After 3-5 days you should have completed the opioid switch to methadone.
Methadone is 2.5 to 15 times more potent than morphine.

To make a complete switch to methadone

1. Calculate the total oral morphine requirement (or oral morphine equivalent (OME), if using a different opioid) over the previous 48 hours and calculate the average 24-hour requirement. Do not include breakthrough doses for incident pain. When calculating OME always use the lowest conversion dose.
2. Reduce the total oral daily dose OME by 30-50% to account for incomplete cross tolerance.
3. Convert the final calculated oral morphine daily dose to oral methadone daily dose by dividing by 15 (most guides say 10 so this is a cautious approach).
4. Divide this into three daily doses. (As a rule, the initial dose should not usually exceed 10 mg 3x per day in an adult/patient over 50 kg, 5 mg 3x per day in child/patient under 50 kg). Initially give either 2 or 3 doses/24 hours.
5. 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.
   Consider using an alternative short acting opioid (such as Oramorph) for breakthrough pain management and consider reduction of the previous breakthrough dose to 50%.

Monitor closely for at least the first 72 hours and be cautious with any dose increments during this period. Generally, dose increments should not exceed 20% of previous dose.

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.

Converting oral methadone to SC/IV or CSCI/CIVI methadone

- Approximate dose ratios for switching between oral dosage and parenteral intravenous/ subcutaneous form 2:1 (oral:parenteral).
- Calculate the total daily dose of oral methadone and halve it (50%). This will be the 24hour parenteral/subcutaneous methadone dose.
- Seek specialist guidance if mixing with any other drug.
- If CSCI methadone causes a skin reaction, consider doubling the dilution and changing the syringe every 12 hours.
- Administer IV methadone slowly over 3-5 minutes.

Notes:

- Not licensed for use in children.
- Methadone is a racemic mixture: L-isomer, analgesic active (levomethadone; L-polamidon®); R-isomerunknown action.
- In some countries levomethadone is available. It has a different strength to methadone.
- Data on methadone in paediatric patients is limited; known to have wide inter-individual pharmacokinetic variation.
- Use methadone with caution, as methadone's effect on respiration lasts longer than analgesic effects.
- Side effects are the same as for all strong opioids.
- Following concerns regarding methadone and sudden death from prolongation of QT interval or torsade de pointes (especially at high doses) it is recommended that patients have an ECG prior to initiation of treatment and regularly whilst on methadone, particularly if they have any risk factors or are having intravenous treatmentwith methadone.
- Opioid antagonists' naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent individuals. Naloxone will also antagonise the analgesic, CNS and respiratory depressant effects of methadone.
- Methadone has the potential for a number of significant drug interactions. Drugs that induce cytochrome P450 3A4 enzymes (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin and some HIV drugs) will increase the rate of metabolism of methadone and potentially lead to reduced serum levels. Drugs that inhibit the system (e.g. amitriptyline, ciprofloxacin, fluconazole) may lead to increased serum levels of methadone.
- Renal impairment: if severe (i.e.GFR <10 ml/min or serum creatinine >700 mmol/l) –reduce methadone dose by 50% and titrate according to response. Significant accumulation is not likely in renal failure, as elimination is primarily via the liver.
- As methadone has a long half-life, infusion of naloxone may be required to treat opioid overdose.
- Available as: linctus (2 mg/5 mL), mixture (1 mg/mL), oral solution (1 mg/mL, 5 mg/mL, 10 mg/mL, and 20 mg/mL), tablets (5 mg), and injection (10 mg/mL,50 mg/mL, 50 mg/2 mL).
- Schedule 2 CD.

Evidence: [235, 280, 337, 338, 340, 346, 420, 663-678]

Methylnaltrexone

Use:

- Opioid-induced constipation when the response to other laxatives alone is inadequate and other relevant factors have been / are being addressed.

Dose and routes
SC (usual route) or IV bolus:

- **Child 1month– 12 years:** 0.15 mg/kg (maximum 8 mg) as a single dose
- **Child >12 years: with weight 38-61 kg:** 8 mg as a single dose
- **Child >12 years: with weight 62-114 kg:** 12 mg as a single dose
- **Child >12 years:** but with body weight less than 38 kg, use 0.15 mg/kg.

A single dose may be sufficient. However repeat doses may be given with a usual administration schedule of a single dose every other day. Doses may be given with longer intervals, as per clinical need. Patients may receive 2 consecutive doses (24 hours apart) only when there has been no response (no bowel movement) to the dose on the preceding day. (30-50% of patients given methylnaltrexone have a bowel movement within 4 hours, without loss of analgesia).

Notes:

- μ-opioid receptor antagonist that acts exclusively in the peripheral tissues including the GI tract (increasing bowel movement and gastric emptying) and does not affect the central analgesic effects of opioids.
- Not licensed for use in children or adolescents less than 18 years.
- Not licensed for IV administration – usual route is SC.
- Methylnaltrexone is contraindicated in cases of known or suspected bowel obstruction other than that caused by opiate-induced constipation.
- The onset of effect may be within 15-60 minutes.
- Common side-effects include abdominal pain/colic, diarrhoea, flatulence and nausea.
- If administered by SC injection rotate the site of injection. Do not inject into areas where the skin is tender, bruised, red or hard.
- Constipation in palliative care is usually multifactorial and other laxatives are often required in addition.
- Reduce dose by 50% in severe renal impairment.
- Does not cross blood brain barrier.
- Available as single use vial 12 mg/0.6 ml solution for SC injection (Relistor$^{(R)}$)

Evidence: [337, 521, 679-684]

Metoclopramide

To minimise the risk of neurological side effects associated with metoclopramide, the EMA in 2013 issued the following recommendations:**(NB use of metoclopramide in palliative care was excluded from these recommendations HOWEVER caution should be exercised nevertheless)**.

Use of metoclopramide is contraindicated in children younger than 1 year.

In children aged 1-18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established postoperative nausea and vomiting, and only when other treatments do not work or cannot be used.

Metoclopramide should only be prescribed for short term use (up to 5 days).

Use

- Antiemetic if vomiting caused by gastric compression or hepatic disease.
- Prokinetic for slow transit time (not in complete obstruction or with anticholinergics).
- Hiccups.

Dose and routes
By mouth, IM injection, SC injection or IV injection (over at least 3 minutes):

- **Neonate:** 100 microgram/kg every 6–8hours (by mouth or IV only).
- **Child 1 month–11 months and body weight up to 10 kg:** 100 microgram/kg (maximum 1 mg/dose) twice daily.
- **Child 1–18 years:** 100-150 microgram/kg repeated up to 3 times daily. The maximum dose in 24 hours is 500 microgram/kg (maximum 10 mg/dose; 30 mg per day).

If preferred the appropriate total daily dose may be administered as a continuous SC or IV infusion over 24 hours.

Notes:

- Not licensed for use in infants less than 1 year of age. Tablets not licensed for use in <15 years (<61 kg).
- Not licensed for continuous IV or SC infusion.
- Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. With metoclopramide, dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it.
- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.
- Oral liquid formulations should be given via a graduated oral syringe to ensure dose accuracy in children. The oral liquid may be administered via an enteral feeding tube. There is no specific information on jejunal administration. Administer using the above method and monitor for efficacy.
- Available as: tablets (10 mg), oral solution (5 mg/5 mL) and injection (5 mg/mL).

Evidence: [88, 89, 206, 337-339, 345, 420, 421, 423, 425, 685-688]

Metronidazole topically

Use:

- Odour caused by anaerobic bacteria associated with wounds or lesions.

Dose and routes
By topical application:

- Apply to clean wound 1–2 times daily and cover with non-adherent dressing.
- Cavities: smear gel on paraffin gauze and pack loosely.

Notes:

- Off label use.
- Anabact® not licensed for use in children < 12 years.
- Metrogel® not licensed for use with children.
- Available as: cream and gel (Anabact® 0.75%, Metrogel® 0.75%) or liquid.

Evidence: [337, 338, 689, 690]

Miconazole oral gel

Use:

- Oral and intestinal fungal infection.

Dose and routes
By mouth:
Prevention and treatment of oral candidiasis

- **Neonate:** 1mL 2-4 times a day smeared around inside of mouth after feeds.
- **Child 1 month–1 year:** 1.25 mL 4 times daily smeared around inside of mouth after food.
- **Child 2–17 years:** 2.5 mL 4 times daily after meals; retain near lesions before swallowing (orthodontic appliances should be removed at night and brushed with gel).

Prevention and treatment of intestinal candidiasis

- **Child 4 months – 17 years:** 5 mg/kg 4 times daily; max. 250 mg (~10 mL) 4 times daily.

Notes:

- Use after food and retain near lesions before swallowing.
- Treatment should be continued for 7 days after lesions have healed.
- Not licensed for use in children under 4 months or during the first 5-6 months of life of an infant born preterm.
- Infants and babies: The gel should not be applied to the back of the throat due to possible choking. The gel should not be swallowed immediately but kept in the mouth as long as possible.
- Contraindicated in infants with impaired swallow.
- Available as: oral gel (20 mg per gram or 124 mg per 5 mL~ 24 mg/mL) in 15 g and 80g tube.
- A buccal tablet of miconazole is now available. Indicated for the treatment of oropharyngeal candidiasis in immunocompromised adults, Loramyc(R)
  50 mg muco-adhesive buccal tablets should be applied to the upper gum just above the incisor tooth once daily for 7-14 days. Currently no experience in children but licensed in USA for child >16 years. May be an option for adolescents.
- Note increased INR/ bleeding has been reported with concomitant use of buccal miconazole and oral anticoagulants.

Evidence: [338, 691-693]

Midazolam

Use:

- Status epilepticus and terminal seizure control.
- Management of anxiety/agitation associated with symptoms at the end of life.
- Anxiety associated with dyspnoea.
- Adjuvant for pain of cerebral irritation.

Dose and routes

Drug doses are quite different depending on underlying disease (i.e. children with cancer or organ failure) and children with severe neurological impairment (SNI). Use lower doses for children with cancer or organ failure and higher doses for children with SNI.

*By SC or IV infusion over 24 hours for **seizure control at end of life**:*

- **Neonate** - **Child 18 years:** Initial dose 1-3 mg/kg/24 hours increasing up to 7 mg/kg/24 hours (maximum 60 mg/24 hoursor 150 mg/24 hours in specialist units for patients with refractory epilepsy).

Seek specialist advice and consider addition of other agents such as phenobarbital if midazolam is not effective.

*Buccal or Intranasal doses for **status epilepticus**:*

- **Neonate:** 300microgram/kg as a single dose, repeated once if necessary.
- **Child 1–2 months:** 300microgram/kg (maximum initial dose 2.5mg), repeated once if necessary.
- **Child 3 months–11 months:** 2.5mg, repeated once if necessary.
- **Child 1–4 years:** 5mg, repeated once if necessary.
- **Child 5–9 years:** 7.5mg, repeated once if necessary.
- **Child 10–17 years:** 10mg, repeated once if necessary.

By buccal or intranasal administration for ***status epilepticus,*** wait 10minutes before repeating dose. NB -In single dose for seizures, midazolam is twice as potent as rectal diazepam. For patients who usually receive rectal diazepam for management of status, consider an initial dose of buccal midazolam that is 50% of their usual rectal diazepam dose to minimise the risk of respiratory depression

Conscious sedation *(to be administered 30-60 minutes before a procedure; or to be administered for terminal haemorrhage in conjunction with an opiate):*

By oral administration

- **Child:** 500 micrograms/kg (maximum 20 mg) as a single dose

By buccal or intranasal administration

- **Child 6 months-9years**: 200-300micrograms/kg (maximum 5 mg) as a single dose
- **Child 10-17years**: 6-7 mg as a single dose

By rectum

- **Child 6 months–11 years:** 300–500 micrograms/kg (maximum 20 mg) as a single dose

By intravenous or subcutaneous injection
The dosages below are based on the BNFc [338]. However research evidence and adult formularies [340] suggests that buccal/intranasal and subcutaneous injections have very similar bioavailability. Many units therefore will use doses of 100 micrograms/kg.

- **Child 1 month–5 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased, if necessary, in small steps to maximum total dose per course; maximum 6 mg per course.

- **Child 6–11 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased, if necessary, in small steps to maximum total dose per course; maximum 7.5 mg per course.

- **Child 12–17 years:** Initially 25–50 micrograms/kg, to be administered over 2–3 minutes, 5–10 minutes before procedure, dose can be increased, if necessary, in small steps to maximum total dose per course; maximum 10 mg per course.

*For **anxiety/ agitation/ dyspnoea**:*

Use 25-50% of the conscious sedation dose.

Notes
- Buccal (Buccolam oromucosal solution) midazolam is not licensed for use in infants less than 3 months of age. Midazolam injection is not licensed for use in seizure control or anxiety. Not licensed for use in children less than 6 months for premedication and conscious sedation.
- The range of potential indications for midazolam in paediatric palliative care is very wide, but most are not licensed in infants in children. Please see product literature.
- Recommended SC/IV doses vary enormously in the literature. If in doubt, start at the lowest recommended dose and titrate rapidly.
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 mins. Half life 2-5 hours. For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Onset of action by oral or gastrostomy route 10-30 minutes. If enteral tube administration is indicated, the oral liquid or injection can be used.
- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Both high and low doses can lead to paradoxical agitation.
- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency.
- Important drug interactions: Midazolam is a major substrate of CYP3A4. Please refer to current edition of BNF for significant drug interactions. Fatalities have occurred after concurrent administration with higher than approved doses of olanzapine
- Available as: oral solution (2 mg/mL special import USA, unlicensed), buccal liquid (pre-filled oral syringes 10 mg in 2 mls; 7.5 mg in 1.5 mls; 5 mg in 1 mL; 2.5 mg in 0.5 mlsBuccolam$^{(R)}$), and injection 1mg/mL, 2mg/mL, 5mg/mL).
  Other oral and buccal liquids (e.g. Epistatus$^{(R)}$ 10 mg/ml) are also available from 'specials' manufacturers or specialist importing companies (unlicensed).

- The buccal and oral formulations available may differ in strength – take care with prescribing.
  Schedule 3 CD (CD No Register Exempt Safe Custody)

Evidence: [59, 63, 64, 190, 191, 338, 341, 693-698]

Morphine

Use:

- Major opioid.
- First line opioid for pain.
- Dyspnoea.
- Cough suppressant

Dose and routes:
Opioid naive patient: Use the following starting doses. (The maximum dose stated applies to **starting** dose only).
Opioid conversion: Convert using OME (Oral Morphine Equivalent) from previous opioid.

By mouth or by rectum

- **Neonate:** Initially 25-50 micrograms/kg every 6-8 hours adjusted to response
- **Child 1–2 months:** Iinitially 50 micrograms/kg every 4 hours, adjusted according to response
- **Child 3–5 months:** Initially 50-100micrograms/kg every 4 hours, adjusted according to response
- **Child 6–11 months:** Initially 100-200 micrograms/kg every 4 hours, adjusted according to response
- **Child 1–11 years:** Iinitially 200–300 micrograms/kg (initial maximum 5-10 mg) every 4 hours, adjusted according to response
- **Child 12–17 years:** Iinitially 5–10 mg every 4 hours, adjusted according to response

By single SC injection or IV injection (over at least 5 minutes):

- **Neonate:** Initially 25 micrograms/kg every 6-8 hours adjusted according to response.
- **Child 1-5months:** Initially 50-100micrograms/kg every 6 hours adjusted according to response.
- **Child 6 months-1 years:** Initially 50-100micrograms/kg every 4 hours adjusted according to response.
- **Child 2-11 years:** Initially 100 micrograms/kg every 4 hours adjusted according to response, maximum initial dose of 2.5 mg.
- **Child 12-17 years:** Initially 2.5-5 mg every 4 hours adjusted according to response (maximum initial dose of 20 mg/24 hours).

By continuous SC or IV infusion:

- **Neonate:** 120 micrograms/kg/24hours adjusted according to response,
- **Child 1-2 months:** 240 micrograms/kg/24hours adjusted according to response,
- **Child 3 months–17 years:** 480 micrograms/kg/24hours (maximum initial dose of 20 mg/24 hours) adjusted according to response.

Breakthrough pain

- For breakthrough pain use 10-16% of total daily morphine dose every 1-4 hours as needed.
- Contact the medical palliative team if someone has needed three doses consecutively as they will need a review of their pain control.

Dyspnoea

30-50% of the dose used for pain.

Notes:

- *Oramorph*® solution not licensed for use in children under 1 year; *Oramorph*® unit dose vials not licensed for use in children under 6 years; *Sevredol*® tablets not licensed for use in children under 3 years; *Filnarine*® SR tablets not licensed for use in children under 6 years; *MST Continus*® preparations licensed to treat children with cancer pain (age-range not specified by manufacturer); *MXL*® capsules not licensed for use in children under 1 year; suppositories not licensed for use in children.
- Caution in renal or hepatic impairment. Reduce dose and/or interval frequency.
- Where opioid substitution or rotation is to morphine: use oral morphine equivalency (OME).
- Particular side effects include urinary retention and pruritus in paediatric setting, in addition to the well recognised constipation, nausea and vomiting.
- Morphine toxicity often presents as myoclonic twitching.
- Rectal route should be avoided if possible, and usually contraindicated in children with low platelets and/or neutropenia.
- In an emergency, when oral intake not appropriate, MST tablets can be administered rectally.
- Administration via enteral feeding tubes: For immediate pain relief use oral solution; no further dilution is necessary for intragastric administration. For administration via a jejunostomy the oral solution should be diluted with an equal volume of water. The tube must be flushed well following dosing to ensure that the total dose is delivered. For sustained pain relief, use MST Continus sachets (via gastrostomy only), dispersed in at least 10 mL of water. Flush the tube well following dosing to ensure that the total dose is delivered. Note that any granules left in the tube will break down over a period of time and a bolus of morphine will be delivered when the tube is next flushed; this has resulted in a reported fatality. Ensure that dose prescribed can be administered using whole sachets when possible. Use of Zomorph capsules opened to release the granules should be done with caution in children due to issues with dose accuracy and the granules should only be administered via an adult size gastrostomy.

Available as: (all Schedule 2 CD except oral solution of strength 10 mg in 5 ml)

- Tablets (10 mg, 20 mg, 50 mg).
- Oral solution (10 mg/5 mL (POM), 100 mg/5 mL).
- Modified release tablets and capsules 12 hourly (5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release suspension 12 hourly (20 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release capsules 24hourly (30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 200 mg).
- Suppositories (10 mg) – 0ther strengths may be available from specials manufacturers.
- Injection (1 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL and 30 mg/mL).

Evidence: [9, 280, 337-339, 341, 345, 473, 490, 568, 699-718]

Nabilone

Use:

- Nausea and vomiting caused by cytotoxic chemotherapy (not first or second line therapy).
- For nausea and vomiting unresponsive to conventional antiemetics.

Dose and routes
By mouth:

- **Child <18 kg:** 0.5 mg twice a day
- **Child 18-30 g:** 1 mg twice a day
- **Child >30 kg:** 1 mg three times a day
- **Adult dose:** 1–2 mg twice a day (maximum dose 6 mg/day in 2-3 divided doses)

Notes:

- Not licensed for use in children.
- Nabilone is a synthetic cannabinoid.
- Individual variation requiring close medical supervision on commencement and dose adjustments.
- The effects of Nabilone may persist for a variable and unpredictable period of time following its oral administration.
- Side effects include somnolence and dizziness
- Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of treatment.
- For specialist use only.
- Available as: capsules (250 microgram, 1 mg). Schedule 2 controlled drug.

Evidence: [337, 338, 340, 719-721] ARE

Naloxone

Use:

- Emergency use for reversal of opioid-induced respiratory depression or acute opioid overdose.

Dose and routes

Complete reversal of respiratory depression due to acute opioid overdose

By intravenous injection:
(**Review diagnosis; further doses may be required if respiratory depression deteriorates)**

- **Neonate – Child 11 years:** 100 micrograms/kg; if no response repeat at intervals of 1 minute until a maximum of 2 mg administered.
- **Child 12-17 years:** Initially 400 micrograms, then 800 micrograms for up to 2 doses at 1 minute intervals if no response to preceding dose, then increased to 2 mg for 1 dose if still no response (4 mg dose may be required in seriously compromised patients).

By continuous intravenous infusion, adjusted according to response

- **Neonate – Child 17 years:** Rate adjusted according to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour),
- ***The initial resuscitative intravenous injection dose is that which maintained satisfactory self ventilation for at least 15 minutes.***

Notes

- Potent opioid antagonist.
- Naloxone has a short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.
- Important: Only give by subcutaneous or intramuscular routes if intravenous route is not feasible; intravenous administration has more rapid onset of action.
- Also see methylnaltrexone.
- Naloxone acts within 2 minutes of IV injection and within 3-5 minutes of SC or IM injection.
- Although oral availability of naloxone is relatively low, be alert for opioid withdrawal symptoms, including recurrence of pain, at higher doses.
- Available as: injection (20 microgram/mL, 400 microgram/mL, 1 mg/mL).

Evidence: [338, 722, 723] ARE

Naproxen

Uses:

- Non-steroidal anti-inflammatory agent analgesic; relief of symptoms in inflammatory arthritis and treatment of acute musculoskeletal syndromes.

Dose and route:
By mouth

- **Child 1 month-17 years:** 5.0-7.5 mg/kg/dose twice daily (maximum 1 g/ day)

Doses up to 10 mg/kg twice daily (not exceeding 1 g daily) have been used in severe conditions. High doses should ideally be used only for a short period. In general, use the lowest effective dose for the shortest treatment duration possible.

Notes:

- Naproxen is licensed for use from 5 years of age for juvenile idiopathic arthritis; not licensed for use in children less than 16 years for other conditions.
- Naproxen is contraindicated in patients with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- Use with caution in renal, cardiac or hepatic failure as this may cause a deterioration in renal function; the dose should be kept as low as possible and renal function monitored. Avoid use if GFR <20ml/min/1.73m2 and in those with severe hepatic or cardiac failure.
- Generally naproxen is regarded as combining good efficacy with a low incidence of side-effects.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults COX-2 selective inhibitors, diclofenac (150mg daily) and ibuprofen (2.4g daily) are associated with an increased risk of thrombotic events (e.g. myocardial infarction and stroke). Naproxen (in adults 1g daily) is associated with a lower thrombotic risk. The greatest risk may increase with dose and duration of exposure so the lowest effective dose should be used for the shortest possible duration of time.
- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects – piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac and naproxen are associated with intermediate risk and ibuprofen with the lowest risk. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur and can be significant.
- Other potential side-effects include headache, dizziness, vertigo, fluid retention and hypersensitivity reactions.
- The anti-pyretic and anti-inflammatory actions of naproxen may reduce fever and inflammation therefore reducing their utility as diagnostic signs.
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Naproxen is a substrate of CYP1A2 and CYP2C8/9 and can increase the plasma concentrations of methotrexate and lithium.
- For administration via an enteral feeding tube, use the oral suspension if available. Naproxen tablets may be crushed before administration and can be mixed with water for administration via a feeding tube. However, naproxen is poorly soluble in water and the tablet must be crushed to a fine powder before mixing with water to avoid tube blockage.

There may be better choices of NSAID if administration via a feeding tube is necessary and oral suspension is not available. Enteric coated naproxen tablets should be swallowed whole and NOT be crushed or chewed. Naproxen should be taken with or after food.

- Available as: tablets 250 mg and 500 mg; enteric coated tablets 250 mg, 375 mg and 500 mg; oral suspension 25 mg/mL .

Evidence: [337, 338, 340, 345]

Nystatin

Use:

- Oral and perioral fungal infection.

Dose and routes
By mouth:

- **Neonate:** 100 000units 4 times a day.
- **Child 1 month-1 year:** 200 000 units 4 times a day.
- **Child 2-17 years:** 400-600 000 units 4 times a day.

Notes:

- Licensed for use in all ages. Neonates – nystatin is licensed for prophylaxis against oral candidosis at a dose of 1ml daily.
- Retain near lesions before swallowing.
- Administerafter food or feeds. If possible, divide the dose between both sides of the mouth.
- Treatment for 7 days and should be continued for 48 hours after lesions have healed.
- Available as: oral suspension 100 000 units/mL, 30 mL with pipette.

Evidence: [338, 509, 724]

Octreotide

Use:

- Bleeding from oesophageal or gastric varices.
- Nausea and vomiting.
- Intestinal obstruction.
- Intractable diarrhoea.
- Hormone secreting tumours, ascites, bronchorrhoea.

Dose and routes
By subcutaneous injection

- **Neonate:** Initially 2–5 micrograms/kg every 6–8 hours, adjusted according to response; increased if necessary up to 7 micrograms/kg every 4 hours, dosing up to 7 micrograms/kg may rarely be required.
- **Child 1 month-17 years:** Initially 1–2 micrograms/kg every 4–6 hours, adjusted according to response; increased if necessary up to 7 micrograms/kg every 4 hours, dosing up to 7 micrograms/kg may rarely be required.

By continuous intravenous or subcutaneous infusion

- **Child 1 month-17 years:** 1 microgram/kg/hour. Higher doses may be required initially. When there is no active bleeding reduce dose over 24 hours. Usual maximum dose is 50 micrograms/hour.

Notes:

- Not licensed for use in children.
- Octreotide is a synthetic analogue of somatostatin with a longer duration of action which acts as an inhibitory hormone throughout the body but particularly the gastro-enterohepatic system, increasing water and electrolyte absorption.
- Monitor glucose levels if used in a non end of life condition.
- Administration: for IV injection or infusion, dilute with sodium chloride 0.9% prior to administration. Check the manufacturer's recommendations regarding dilution. For SC 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). For SC infusion dilute with 0.9% NaCl.
- Avoid abrupt withdrawal (associated with biliary colic and pancreatitis).
- Available as: injection for SC or IV administration (50 micrograms/mL, 100 micrograms/mL, 200 micrograms/mL, 500 micrograms/mL*)*.
  Also available as depot injection for IM administration every 28 days (10 mg, 20 mg and 30 mg SandostatinLar^{R}). Recommend specialist palliative care advice.

Evidence: [338, 420, 725]

Olanzapine

Uses:

- Psychoses; delirium; agitation; anorexia when all other treatments have failed.
- Nausea and vomiting.

Dose and route**:**
Oral:

Psychoses / mania
Child <12 years and <25 kg: Initial dose 2.5 mg at night
Child <12 years and >25 kg: Initial dose 2.5-5 mg at night.
Child 12-17 years: initial dose 5 mg at bedtime.

Increase gradually as necessary and as tolerated to a maximum of 20mg/day given usually as a single dose at night. Can be given as twice daily dose if needed.

Agitation/delirium
Child <12 years: Initial dose 1.25 mg at night and as required,
Child 12-17 years: Initial dose 2.5 mg at night and as required.

Increase gradually as necessary and as tolerated tomaximum 10mg/day.

Nausea and vomiting; anorexia
Child <12 years: Initial dose 1.25 mg (or 0.625 mg if 2.5 mg tablets can be cut into quarters) at night and PRN,
Child 12-17 years: Initial dose 1.25-2.5 mg at night and as required.

Dose may be increased as necessary and as tolerated to a suggested maximum of 7.5 mg/day.

Notes:

- Olanzapine is not licensed for use in children and adolescents less than 18 years of age although there is general acknowledgement of 'off-label' use in adolescents for the treatment of psychosis and schizophrenia and mania associated with bipolar disorder.
- Use in the treatment of agitation/delirium, nausea and vomiting and anorexia in palliative care are all 'off-label' indications.
- Olanzapine is an atypical (second generation) antipsychotic agent and antagonist of dopamine D1, D2, D4, 5-HT2, histamine- 1-, and muscarinic-receptors.
- Olanzapine has 5x the affinity for $5HT_2$ receptors than for D_2 receptors resulting in fewer extrapyramidal sideeffects.
- Activity of olanzapine at multiple receptors is similar to levomepromazineand therefore it has a potential role in the treatment of nausea and vomiting refractory to standard medication.
- Use with caution in those with cardiovascular disease or epilepsy (and conditions predisposing to seizures as lowers seizure threshold).
- Very common (> 10% patients) adverse effects: weight gain; elevated triglyceride levels; increased appetite; sedation; increased ALT and AST levels; decreased bilirubin; increased

GGT and plasma prolactin levels. Common (1-10% patients) adverse effects: elevated cholesterol levels; dry mouth.

- Rare but potentially serious adverse effects include neuroleptic malignant syndrome, cardiovascular disease, severe respiratory disease and bone marrow depression, hepatitis, pancreatitis. Hyperglycaemia and sometimes diabetes can occur.
- Dose titration should be slow to minimise sedation.
- A greater magnitude of weight gain and lipid and prolactin alterations have been reported in adolescents compared to adults. If prolonged use is likely, consider the monitoring of blood lipids, weight, fasting blood glucose and prolactin. Consider an ECG and BP measurement before initiation.
- Consider lower starting dose (maximum 5mg in adults) in patients with renal and/or hepatic impairment.
- Olanzapine has good oral bioavailability with peak plasma concentrations occurring within 5-8 hours. Absorption is not affected by food. Long elimination half-life of ~33 hours. Onset of actions is hours-days in delirium; days-weeks in psychoses.
- Olanzapine does not inhibit or induce the main CYP450 isoenzymes. Olanzapine is metabolised by CYP1A2 therefore drugs/substances that specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine e.g. carbamazepine, fluvoxamine, nicotine.
- Orodispersible tablets: place in mouth where the tablet will rapidly disperse in saliva **or** disperse in a full glass of water (or other drink) immediately before administration. May be dispersed in water for administration via a NG or gastrostomy feeding tube. There are no specific reports of jejunal administration of olanzapine. Administer using the above method. Monitor for loss of efficacy or increased side-effects. Some anecdotal experience that 5mg orodispersible tablets may be halved to give a 2.5 mg dose. Halve immediately before administration and do not save the remaining half for a future dose
- Coated tablets: swallow whole with liquid or crushed and mixed with soft food.
- Orodispersible tablets contain aspartame and may be harmful for people with PKU.
- Coated tablets contain lactose.
- Available as: tablets 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg; orodispersible tablets / lyophilisate 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg.

Evidence: [337, 338, 726-742]

Omeprazole

Use:

- Gastro-oesophageal reflux.
- Acid related dyspepsia.
- Gastrointestinal prophylaxis (e.g. with combination NSAID/steroids).
- Treatment of duodenal and gastric ulcers.

Dose and routes
By mouth:

- **Neonate:** 700 microgram/kg once daily; increase if necessary to a maximum of1.4 mg/kg once daily (max dose: 2.8 mg/kg once daily).
- **Child 1 month–1 year:** 700 microgram/kg once daily; increase if necessary to a maximum of 3 mg/kg once daily (max dose: 20 mg once daily).
- **Child body weight 10–19 kg:** 10 mg once daily; increase if necessary to a maximum of 20 mg once daily.
- **Child body weight 20 kg and above:** 20 mg once daily; increase if necessary to a maximum of 40 mg once daily.

Intravenous (by infusion over 20-30 minutes)

- **Child 1 month -11 years:** initially 500 micrograms/kg (max:20 mg) once daily, increased, if necessary to 2 mg/kg (max: 40 mg) once daily.
- **Child 12-17 years:** 40 mg once daily.

Notes:

- Oral formulations are not licensed for use in children except for severe ulcerating reflux oesophagitis in children > 1 year.
- Infusion not licensed for use in children under 12years.
- Many children with life limiting conditions have gastro-oesophageal reflux disease and may need to continue with treatment long term.
- Can cause agitation.
- Occasionally associated with electrolyte disturbance.
- MHRA safety warning 2015: there is a very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs.
- For oral administration tablets can be dispersed in water or with fruit juice or yoghurt. Capsules can be opened and mixed with fruit juice or yoghurt.
- Administer with care via enteral feeding tubes to minimise risk of blockage. Capsules may be opened and contents dispersed in 8.4% sodium bicarbonate for administration. Dispersible tablets disintegrate to give a dispersion of small granules. The granules settle quickly and may block fine-bore feeding tubes (less than 8Fr). For administration via small bore tubes use of an oral suspension (unlicensed) is recommended. Omeprazole is absorbed when administered into the jejunum with no reduction in bioavailability. Choice of formulation depends on the size of tube.
- Available as: gastoresistant tablets (MUPS) tablets (10 mg, 20 mg, 40 mg), capsules (10 mg, 20 mg, 40 mg), intravenous infusion (40 mg) and oral suspension available as an unlicensed special (10 mg in 5ml but other strengths may be available so be careful).

Evidence: [12, 90, 337-339, 345, 616, 743-747]

Ondansetron

Use:

- Antiemetic, if vomiting caused by damage to gastrointestinal mucosa (eg chemotherapy or radiotherapy).
- Pure 5HT3 antagonist, so receptor profile is complementary to levomepromazine – consider for N&V that breaks through despite regular levomepromazine.
- Has been used inmanaging opioid induced pruritus.
- For severe gastroenteritis.

Dose and routes

Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting.

Terminal half life is 3 hours. Cleareance reduced in younger infants -75% in neonates and 50% at 3 months. Children <4 months must be closely monitored.

By intravenous infusion over at least 15 minutes

- **Child 6 months–17 years:** e*ither* 5 mg/m^2 immediately before chemotherapy (max. single dose 8 mg), then give by mouth, *or* 150 micrograms/kg immediately before chemotherapy (max. single dose 8 mg) repeated every 4 hours for 2 further doses, then give by mouth; max. total daily dose 32 mg

By mouth following intravenous administration

Note:
Oral dosing can start 12 hours after intravenous administration

- **Child 6 months–17 years:**
- Body surface area less than 0.6 m^2*or* body weight 10 kg or less: 2 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)
- Body surface area 0.6 m^2 – 1.2 m^2 or greater *or* body weight over 10 kg: 4 mg every 12 hours for up to 5 days (max. total daily dose 32 mg)
- Body surface area greater than 1.2 m^2*or* body weight over 40 kg: 8mg every 12 hours for up to 5 days (max. total daily dose 32 mg)

Nausea and vomiting

By mouth or slowintravenous injection over 2-5 minutesor by intravenous infusion over 15 minutes

- **Child 1-17 years:** 100 microgram/kg/dose every 8-12 hours. Maximum single dose 4 mg.

Notes:

- Ondansetron injection is licensed for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of post operative nausea and vomiting (PONV) in children (as a single dose) aged ≥1 month. Oral ondansetron is licensed from 6 months of age for the management of CINV but the oral formulation is not recommended for PONV in children due to a lack of data.
- Onset of action PO <30 mins, IV <5 mins and duration 12 hours.
- Contraindicated in congenital long QT syndrome. Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.
- Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- Powerfully constipating.
- Headache is a common adverse effect.
- Repeat IV doses of ondansetron should be given no less than 4 hours apart.
- For intravenous infusion, dilute to a concentration of 320–640 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% or Ringer's Solution; give over at least 15 minutes.
- Oral solution may be administered via an enteral feeding tube. However be aware of the large sorbitol content of high doses. There is no specific data on jejunal administration. Administer using the above method. Monitor for loss of efficacy or increased side-effects.
- Can be give via subcutaneous infusion via syringe driver.
- Available as: tablets (4 mg, 8 mg, orodispersible films/tablets (4 mg, 8 mg), oral syrup (4 mg/5 mL), injection (2 mg/mL, 2 mL and 4 mL amps). 16mg suppositories also available.

Source: [205, 207, 338, 339, 341, 471, 686, 748-750]

Oxycodone

Use:

- Alternative opioid for severe pain
- Pain of all types unless opioid insensitive

Dose and routes

Opioid switch: Convert using OME (Oral Morphine Equivalent) from previous opioid.

Use the following **starting** doses in the **opioid naive** patient. The maximum dose stated applies to the **starting** dose only.

By mouth:
Conversion

- Oral Morphine 1.5: Oral Oxycodone 1
- i.e. 15 mg Morphine: 10 mg Oxycodone

- **Child 1 month–11 years:** Initial dose 200 micrograms/kg (maximum single dose 5 mg) every 4 -6 hours.
- **Child 12-17 years:** Initial dose 5 mg every 4-6 hours.

- Titrate as for morphine: Increase dose if necessary, according to severity of pain.

- **m/r tablets Child 8-11 years:** Initial dose 5 mg every 12 hours, increased if necessary
- **m/r tablets Child 12-17 years:** Initial dose 10 mg every 12 hours, increased if necessary.

By intravenous injection, subcutaneous injection or continuous subcutaneous infusion:
Conversion:

- Oral to IV or SC Oxycodone single bolus doseinjection: Divide the oral Oxycodone dose by 1.5(some texts suggest divide by 2 but clinically 1.5 used).
- Oral to a continuous subcutaneous infusion of Oxycodone over 24 hours: Divide the total daily dose of oral Oxycodone by 1.5 (some texts suggest divide by 2 but clinically 1.5 used).
- SC/IV Morphine to SC/IV Oxycodone ratio is approximately1:1. i.e. use same dose.
- Reason behind odd conversion ratio is bioavailability and rounding factors for safety.

Notes:

- Not licensed for use in children less than 12 years of age.
- No neonatal dose available.
- No evidence of any benefit over morphine and significantly more expensive.
- Associated with dose dependant QTc prolongation.
- Available in combination with naloxone as alternative to laxative therapy in opioid-induced constipation Targinact® (Napp) – not licensed in children.
- It is important to prescribe breakthrough analgesia which is 5-10% of the total 24 hour dose, given every 1 to 4 hours.
- It is moderately different from morphine in its structure, making it a hypothetical candidate for opioid substitution.
- Caution in hepatic or renal impairment.

- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with WFI, 0.9% sodium chloride or 5% glucose.
- Oxycodone liquid may be administered via an enteral feeding tube. There is no specific data relating to jejunal administration. Monitor for lack of efficacy or side-effects.
- Safety Information: oxycodone modified release tablets are available as 12-hourly and 24-hourly preparations. Care with prescribing and do not confuse brands.
- Controlled drug schedule 2.
- Available as: capsules (5 mg, 10 mg, 20 mg), oral solution (5 mg/5 mL, 10 mg/mlL and m/r tablets (5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg), injection (10 mg/mL and 50 mg/mL).

Evidence: [337, 338, 340, 345, 385, 487, 751-758]

Oxygen

Use

- Breathlessness caused by hypoxaemia.
- Placebo effect, especially where family feels need to intervene promptly.
- Alternative to air blowing on face.

Dose and routes:
By inhalation through nasal cannula

- Flow rates of 1– 2.5L/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 rateand/or type of mask. 28% oxygen is usually recommended for continuous oxygen delivery.

Notes:

- The evidence to support the use of O2 in non-hypoxemic patients is scant at best, which is why it best to use it in an N of 1 fashion. The patient will say if it works or not. General experience is that response to O2 for the treatment of breathlessness is just as likely/unlikely regardless of the patient's PaO2, so try it and if it doesn't help stop.
- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Where self-report is not possible observation of the work of breathing is a more reliable indicator of breathlessness.
- Frequent or continuous measurement of oxygen saturations may lead to an over-reliance on technical data and distract from evaluation of the child's overall comfort, symptom relief and wellbeing.
- Target oxygen saturations of 92 – 96% may be appropriate in acute illness but are not necessarily appropriate for palliative care. More usual target oxygen saturations are above 92% in long-term oxygen therapy and 88-92% in children at risk of hypercapnic respiratory failure. Lower saturation levels may be tolerated in children with cyanotic congenital heart disease.
- It is important to be clear about the overall aims of oxygen treatment and realistic saturation levels for an individual child, as this will affect decisions about target oxygenation.
- In cyanotic congenital heart disease, oxygen has little effect in raising SaO2 and is not generally indicated. Pulmonary hypertension, in the early stages, may respond to oxygen, so it may be appropriate in the palliative care setting.
- Moving air e.g. from a fan maybe equally effective in reducing the sensation of breathlessness when the child is not hypoxaemic.
- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions. However continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.
- Oxygen administration via a maskor via NIPPV can be claustrophobic and/or damage facial skin. This can be reduced by using a nasal mask. The duration of supply from an oxygen cylinder will depend on the size of the cylinder and the flow rate.

- An oxygen concentrator is recommended for patients requiring more than 8 hours oxygen therapy per day.
- Liquid oxygen is more expensive but provides a longer duration of portable oxygen supply. Portable oxygen concentrators are now also available.
- If necessary, two concentrators can be Y-connected to supply very high oxygen concentrations.
- Higher concentrations of oxygen are required during air travel.
- Home oxygen order forms (HOOF) and further information available from www.bprs.co.uk/oxygen.html
- A secondary supply of oxygen for children spending a prolonged time away from home requires a second HOOF available from the above website e.g. short breaks, holiday or extended periods with other relatives.

Evidence: [54, 337, 338, 340, 759-763]

Pamidronate (Disodium)

Use:

- Adjuvant for bone pain caused by metastatic disease.
- Adjuvant for bone pain due to osteopenia or osteoporosis associated with neuromuscular conditions.
- Tumour-induced hypercalcaemia.
- Treatment of secondary osteoporosis to reduce fracture risk.
- Osteogenesis imperfecta.

NB Seek specialist advice before use.

Dose and routes

For bone pain (metastatic bone disease or osteopenia); secondary osteoporosis:
An effect on pain can be seen within 2 weeks but may need a year before definitive assessment. Continue dosing for as long as effective and tolerated or until substantial decline in performance status.

By IV infusion

- 1 mg/kg as a single dose infused over 4-6 hours repeated monthly as required: concentration not exceeding 90 mg in 250 mL.
  OR
- 1 mg/kg infused over 4-6 hours on 3 consecutive days and repeated every 3 months as required: concentration not exceeding 90 mg in 250 mL.

For malignant hypercalcaemia: **(Seek specialist advice)**

By IV infusion

- 1 mg/kg infused over 6 hours: concentration not exceeding 90 mg in 250 mL. Then repeated as indicated by corrected serum calcium.

For osteogenesis imperfecta

By IV infusion

- In total all patients receive 12 mg/kg over the course of 1 year as:
- 1 day regimen: 1 mg/kg/day on a single day repeated monthly
- 2 day regimen: 1.5 mg/kg/day on 2 consecutive days, repeated every 3 months
- 3 day regimen: 1mg /kg/day on 3 consecutive days, repeated every 3 months
- Usual maximum single dose 90 mg (although occasionally higher doses are seen)
- If there is any concern about the starting dose, 0.5 mg/kg may be considered as the first dose for the first cycle.

Notes:

- Not licensed for use in children. Well tolerated by children, but long term effects unknown.
- Local guidelines vary. Some centres advise DEXA scan and investigations into calcium metabolism before and after treatment. Effectiveness of Pamidronate in bone pain does not necessarily depend on demonstrating osteoporosis, but demonstration that iatrogenic osteopetrosis has not developed afterwards can be reassuring. Flu-like symptoms often accompany first infusion, though typically do not recur with subsequent doses.
- Bisphosphonates have been used for some years in adults with bone metastases. It is becoming clear that they have a role in the wider causes of bone pain seen in children, particularly with neurological conditions.
- Current guidelines suggest initial dose be given as an inpatient. Subsequent doses could be given at home, if the necessary medical and nursing support is available. May have worsening of pain at first.
- IV zoledronic acid can also be used 25-50 microgram/kg/ dose (maximum 4-5 mg) repeated, if necessary, every 6-12 months. Under specialist advice only.
- Oral risedronate and oral alendronate limited use for these indications due to poor and variable bioavailability.
- If the IV route is unavailable, bisphosphonates can be administered by CSCI over 12-24 hours, together with SC hydration.
- Many bisphosphonates are available in different formulations, including oral, although absorption tends to be poor by the oral route and further reduced by food or fluids other than plain water.
- Caution: monitor renal function and electrolytes; ensure adequate hydration.
- Prolonged hypocalcaemia and hypomagnesaemia may occur with concurrent use of aminoglycoside and a bisphosphonate. Consider calcium and vitamin D oral supplements to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases and at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight).
- Risk of renal impairment is increased by concurrent use with other nephrotoxic drugs.
- Risk in adults of atypical femoral fractures, and of osteonecrosis especially of the jaw and the external auditory canal. Not widely reported in children but suggest dental treatment before treatment and good dental hygiene advised. Patient/family education.
- Available as: injection vials for infusion of various volumes, at 3 mg/mL, 6 mg/mL, 9 mg/mL, 15 mg/mL.

Evidence: [325, 337, 340, 764-772]

Paracetamol

(US: Acetaminophen)

Use:

- Mild to moderate pain (step 1 of WHO pain ladder).
- Pyrexia.

Dose:

The recommended indications and doses of paracetamol have been revised to take account of MHRA and Toxbase advice that paracetamol toxicity may occur with doses between 75-150 mg/kg/day (ingestion of over 150 mg/kg/day is regarded as a definite risk of toxicity).

Oral:

- **Neonate 28–32 weeks corrected gestational age:** 20 mg/kg as a single dose then 10-15 mg/kg every 8 - 12 hours as necessary (maximum 30 mg/kg/day in divided doses).
- **Neonates over 32 weeks corrected gestational age:** 20 mg/kg as a singledose then 10-15 mg/kg every 6 - 8 hours as necessary (maximum 60 mg/kg/day in divided doses).
- **Child 1 month–5 years:** 20-30 mg/kg as a single dose then 15-20 mg/kg every 4-6 hours as necessary (maximum75 mg/kg/day in divided doses).
- **Child 6-11 years:** 20-30 mg/kg (max 1 g) as a single dose then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day or 4 g/day in divided doses).
- **Over 12 years:** 15-20 mg/kg (maximum 500 mg -1 g) every 4-6 hours as necessary (maximum 4 g /day in divided doses).

Rectal:

- **Neonate 28–32 weeks corrected gestational age:** 20 mg/kg as a single dose then 10-15 mg/kg every 12 hours as necessary (maximum 30 mg/kg/day in divided doses).
- **Neonates over 32 weeks corrected gestational age:** 30 mg/kg as a single dose then15-20 mg/kg every 8 hours as necessary (maximum 60 mg/kg/day in divided doses).
- **Child1–2 months:** 30 mg/kg as a single dose, then 15-20 mg/kg every 4-6 hours as necessary (maximum 75 mg/kg/day in divided doses).
- **Child 3 months-11years:** 30 mg/kg as a single dose (maximum 1 g) then 15-20 mg/kg every 4-6 hours as necessary (maximum75 mg/kg/day or 4 g/day in divided doses).
- **Over 12 years:** 15-20 mg/kg (maximum 500 mg -1 g) every 4-6 hours as necessary (maximum 4 g/day in divided doses).

IV: as infusion over 15 minutes

- **Preterm neonate over 32 weeks corrected gestational age:** 7.5 mg/kg every 8 hours, maximum 25 mg/kg/day.
- **Neonate:** 10 mg/kg every 4-6 hours (maximum 30 mg/kg/day).
- **Infant and child bodyweight <10 kg:** 10 mg/kg every 4-6 hours (maximum 30 mg/kg/day)
- **Child bodyweight 10-50 kg:** 15 mg/kg every 4-6 hours (maximum 60 mg/kg/day).
- **Bodyweight over 50 kg:** 1 g every 4-6 hours (maximum 4 g/day).

Notes:

- Many children and young people with life limiting illness have low weight for their age. The doses above are therefore quoted mainly by weight rather than age (unlike most of the entries in the BNF and BNFc), in order to minimise risk of over-dosing in this patient group.
- Not licensed for use in children under 2 months by mouth; not licensed for use in preterm neonates by intravenous infusion; not licensed for use in children under 3 months by rectum; doses for severe symptoms not licensed; paracetamol oral suspension 500 mg/5 mL not licensed for use in children under 16 years.
- Oral and licensed rectal preparations are licensed for use in infants from 2 months for post immunisation pyrexia (single dose of 60 mg which may be repeated once after 4-6 hours if necessary), and from 3 months as antipyretic and analgesic.
- IV paracetamol is licensed for short term treatment of moderate pain, and of fever when other routes not possible.
- Consider use of non pharmacological measures to relieve pain, as alternative or in addition to analgesics.
- Hepatotoxic in overdose or prolonged high doses.
- In moderate renal impairment use maximum frequency of 6 hourly: in severe renal impairment maximum frequency 8 hourly.
- Onset of action 15-30 minutes orally, 5-10 minutes IV (analgesia), 30 minutes IV (antipyretic). Duration of action 4-6 hours orally and IV. Oral bioavailability 60-90%. Rectal bioavailability about 2/3 of oral. However, rectal absorption is now known to be erratic and incomplete, and results in slower absorption than oral administration, (except in babies when the oral preparation used rectally speeds absorption compared with suppositories). Elimination is slower in babies under 3 months.
- Dispersible tablets have high sodium content (over 14mmol per tablet), so caution with regular dosing (consider using the liquid preparation instead).
- For administration via an enteral feeding tube: Use tablets dispersed in water for intragastric or intrajejunal administration. If the sodium content is problematic, use the liquid formulation. This can be used undiluted for intragastric administration; however, the viscosity of the paediatric liquid preparations is very high; it is difficult to administer these suspensions via a fine bore tube without dilution. If administering intrajejunally, dilute with at least an equal quantity of water to reduce osmolarity and viscosity.
- For management of feverish illness in children, see updated NICE clinical Guideline CG160. (Consider using *either* paracetamol or ibuprofen in children with fever who appear *distressed* and consider changing to the other agent if distress is not alleviated. But do not use antipyretic agents with the sole aim of reducing body temperature). However, a recent Cochrane systematic review states “there is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone”.
- Available as: tablets and caplets (500 mg), capsules (500 mg), soluble tablets (120 mg, 500 mg), oral suspension (120 mg/5 mL, 250 mg/5 mL), Fastabs 250 mg, suppositories (60 mg, 125 mg, 250 mg, 500 mg and other strengths available from ‘specials’ manufacturers or specialist importing companies) and intravenous infusion (10 mg/mL in 50 mL and 100 mL vials).

Evidence: [337-339, 341, 345, 562, 773-776]WRE

Paraldehyde (rectal)

Use:

- Treatment of prolonged seizures and status epilepticus.

Dose and route:
By rectal administration (**dose shown is forpremixed enema 50:50 with olive oil**)

- **Neonate:** 0.8 mL/kg as a single dose.
- **I month-17 years:** 0.8 mL/kg (maximum 20mL) as a single dose.

Notes:

- Rectal administration may cause skin irritation.
- Contra-indicated in gastric disorders and in colitis.
- Paraldehyde enema for rectal use is an unlicensed formulation and route of administration.
- Available as paraldehyde enema: premixed solution of paraldehyde in olive oil in equal volumes from 'special-order' manufacturers or specialist importing companies.

Evidence: [338, 341, 777-783] WRE

Phenobarbital

Use:

- Adjuvant in pain of cerebral irritation.
- Control of terminal seizures.
- Sedation (soporific and anxiolytic).
- Epilepsy including status epilepticus. Commonly used first line for seizures in neonates (phenytoin or benzodiazepine are the main alternatives).
- Agitation refractory to midazolam in end of life care.

Dose and routes

Status epilepticus / terminal seizures / agitation
Loading doses are not usally necessary unless it is for rapid control of terminal seizures in someone not already on anticonvulsants. This is because in paediatric palliative care it is not often used for emergency seizure control, but for cerebral irritation. Where it is for seizures, it is normally used for prophylaxis or adding it to other anticonvulsants. In those cases there is usually no hurry to get to an effective serum concentration

Loading dose if required
Oral, intravenous or subcutaneous injection:
All ages: 20 mg/kg/dose (maximum 1 g) administered over 20 minutes if by IV or SC injection (but see notes below).

Subcutaneous or intravenous injection or infusion:

- **Neonates for control of ongoing seizures:** 2.5-5 mg/kg once or twice daily as maintenance.
- **Child 1 month-11 years:** 2.5-5 mg/kg (maximum single dose 300 mg) once or twice daily or may be given as a continuous infusion over 24 hours.
- **Child 12-17 years:** 300 mg twice daily or may be given as a continuous infusion over 24 hours.

Epilepsy:
By mouth:

- **Neonates for control of ongoing seizures:** 2.5-5 mg/kg once or twice daily as maintenance.
- **Child 1 month–11 years:** 1–1.5 mg/kg twice a day, increased by 2 mg/kg daily as required (usual maintenance dose 2.5–4 mg/kg once or twice a day).
- **Child 12–17 years:** 60–180 mg once a day.

Notes:

- Licence is only for seizures. Not licensed for agitation in end of life care.
- Single loading dose is required for initiation of therapy if immediate effect is needed; administer via enteral route if possible. Loading dose can be administered intravenously over 20 minutes or as a slow subcutaneous loading dose however the volume of resultant solution will limit the rate at which a subcutaneous bolus can be administered.
- Loading dose used to reach steady state quickly and avoid late toxicity due to accumulation.
- For patients already on oral phenobarbital but needing parenteral treatment, doses equivalent to the patient's usual total daily dose of oral phenobarbital can be used.

- Elimination half life of 2-6 days in adults, 1-3 days in children.
- Phenobarbital induces various enzymes of the CYP450 system and thus may reduce the plasma concentrations of concomitant drugs that are metabolised by this system.
- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- Tablets may be crushed for administration if preferred.
- The liquid preparations may be administered via an enteral feeding tube. For administration via a jejunostomy tube, dilution with water is recommended to reduce the liquid viscosity.
- Use a separate site to commence subcutaneous infusion. SC bolus injections should be avoided because they can cause tissue necrosis due to the high pH.
- It is essential to dilute the injection in 10 times the volume of water for injection before intravenous or subcutaneous injection (i.e. to maximum concentration of 20 mg/mL).
- Available as: tablets (15 mg, 30 mg, 60 mg), oral elixir (15 mg/5 mL) and injection (15 mg/mL, 30 mg/mL, 60 mg/mL and 200 mg/mL). The licensed oral elixir of 15 mg in 5 mL contains alcohol 38% and it is preferable to obtain an alcohol free oral liquid via one of the specials manufacturers. CD Schedule 3 (CD No Register Phenobarbital).

Evidence: [61, 63, 338, 339, 521]

Phenytoin

Use:

- Epilepsy (3rd or 4th line oral antiepileptic) including for status epilepticus.
- Neuropathic pain (effective, at least short term, but not used first line).

Dose

All forms of epilepsy (including tonic-clonic, focal and neonatal seizures) except absence seizures. Neuropathic pain.

Oral or slow IV injection:

- **Neonate:** Initial loading dose by slow IV injection 18 mg/kg **THEN by mouth** 2.5-5 mg/kg twice daily adjusted according to response and plasma phenytoin levels. Usual maximum 7.5 mg/kg twice daily.
- **1 month -11 years:** Initial dose of 1.5-2.5 mg/kg twice daily then adjust according to response and plasma phenytoin levels to 2.5-5 mg/kg twice daily as a usual target maintenance dose. Usual maximum dose of 7.5 mg/kg twice daily or 300 mg daily.
- **12 -17 years:** initial dose of 75-150 mg twice daily then adjusted according to response and plasma phenytoin levels to 150-200 mg twice daily as a usual target maintenance dose. Usual maximum dose of 300 mg twice daily.

Status epilepticus, acute symptomatic seizures:

Slow IVinjection or infusion:

- **Neonate:** 20 mg/kg loading dose over at least 20 minutes, then 2.5-5 mg/kg/dose (over 30 minutes) every 12 hours as a usual maintenance dose in first week of life. Adjust according to response and older babies may need the higher doses. After the first dose, oral doses usually as effective as intravenous in babies over 2 weeks old.
- **1 month – 11 years:** 20 mg/kg loading dose over at least 20 minutes, then 2.5-5 mg/kg twice daily usual maintenance dose.
- **12 -17 years:** 20 mg/kg loading dose over at least 20 minutes, then up to 100 mg (over 30 minutes) 3 to 4 times daily usual maintenance dose.

Notes:

- Licensed status: suspension 90mg in 5mL is a 'special' and unlicensed. Other preparations are licensed for use in children as an anticonvulsant (age range not specified).
- Phenytoin acts as a membrane stabiliser.
- It has a narrow therapeutic index, unpredictable half life, and the relationship between dose and plasma-drug concentration is non-linear. The rate of elimination is also very variable, especially in the first few weeks and months of life. Co-treatment with commonly used drugs can significantly alter the half life.
- Phenytoin has numerous interactions with other drugs due to hepatic enzyme induction. Long term use is associated with significant side effects. It is no more effective than other anti-epileptics and hence not usually used first line, although it does enable rapid titration.
- Continuous ECG and BP monitoring required during IV administration.
- Oral bioavailability 90-95% is roughly equivalent to intravenous, plasma half-life 7-42 hours. Poor rectal absorption.

- Reduce dose in hepatic impairment. Monitor carefully if reduced albumin or protein binding e.g. in renal failure.
- Caution: cross-sensitivity is reported with carbamazepine.
- Avoid abrupt withdrawal.
- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- Before and after administration, flush intravenous line with Sodium Chloride 0.9%.
- For *intravenous injection*, give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute).
- For *intravenous infusion*, dilute to a concentration not exceeding 10 mg/mL with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50mg/minute); complete administration within 1 hour of preparation.
- Prescriptions for oral preparations should include brand name and be of consistent preparation type, to ensure consistency of drug delivery.
- Preparations containing phenytoin sodium are **not** bioequivalent to those containing phenytoin base (such as *Epanutin Infatabs*® and *Epanutin*® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma phenytoin concentration monitoring is recommended.
- Bioavailability may be reduced unpredictably by enteral feeds and/or nasogastric tube feeds, so flush with water to enhance absorption, interrupt enteral feeding for at least 1-2 hours before and after giving phenytoin and maintain similar timings and regimes from day to day. Use the oral suspension for enteral tube administration; dilution with an equal volume of water is recommended for gastrostomy administration. Absorption is exceptionally poor via the jejunal route; plasma concentration should be monitored closely if this route is used. Dilution of the suspension is important as phenytoin suspension is hyperosmolar and may cause diarrhoea when administered into the jejunum.
- Available as tablets (phenytoin sodium 100 mg, generic), capsules (phenytoin sodium 25 mg, 50 mg,100 mg, 300 mg), Epanutin ® Infatabs (chewable tablets of phenytoin base 50 mg), oral suspension (Epanutin®phenytoin base 30 mg/5 mL, and 90 mg/5 mL phenytoin base available as an ‘unlicensed special’), and injection (phenytoin sodium 50 mg/mL generic)

Evidence: [338-341, 345, 397, 754, 784-788], WRE

Phosphate (rectal enema)

Use:

- Constipation refractive to other treatments.

Dose and routes:
Phosphate enema BP Formula B (with standard or long rectal tube):

- **Child 3–6 years:** 45-65 mL once daily.
- **Child 7-11 years:** 65-100 mL once daily.
- **Child 12–17 years:** 100-128 mL once daily.

Fleet^{R}Ready to Use enema:

- **Child 3–6 years:** 40-60 mL once daily.
- **Child 7-11 years:** 60-90 mL once daily.
- **Child 12–17 years:** 90-118 mL once daily.

Notes

- Maintain good hydration and watch for electrolyte imbalance.
- Onset 30 minutes to 6 hours.
- Contraindicated in acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption).
- There have been case reports of hyperphosphataemia and tetany in children following the use of phosphate enemas.
- NICE Guidance CG99 (Constipation in children & Young People) makes a 'Do Not Do Recommendation': 'Do not administer phosphate enemas for disimpaction unless under specialist supervision in hospital / health centre / clinic, and only if all oral medications and sodium citrate have failed'.
- Use only after specialist advice.

Evidence: [337, 338, 789-793], WRE

Pregabalin

Use:

- Epilepsy (focal seizures with or without secondary generalisation)
- Peripheral and central neuropathic pain
- Generalised anxiety disorder

Dose and route:
Epilepsy (adjunctive therapy for partial seizures)

- **Child:** suggested maintenance dose of 5-10 mg/kg/day. Start at low dose and increase gradually every 3-7 days as tolerated. Maximum 600 mg/day given in 2-3 divided doses. Younger children less than 6 years may need up to 15 mg/kg/day.

Neuropathic Pain

- **Child:**
  Day 1-3: 1 mg/kg once a day
  Day 4-6: 1 mg/kg 12 hourly
  Day 7: Increase every 3-7 days by 1 mg/kg until
  1. Effective analgesia reached, or
  2.Side effects experienced, or
  3. Max total daily dose of 6mg/kg/day (although higher dses of 12 mg/kg have been used).

Gabapentin to Pregabalin switch for neuropathic pain
Consult appendix 3

Notes:

- Not licensed for use in children or adolescents less than 18 years of age.
- Licensed in adults as adjunctive therapy for partial seizures, for the treatment of peripheral and central neuropathic pain and for the treatment of generalised anxiety disorder.
- NICE Guidance CG173 (Neuropathic pain in adults) recommends: 'offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment of neuropathic pain, if the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs and consider switching again if the second and third drugs tried are also not effective or not tolerated'.
- MHRA/CHM issued a warning to prescribers in April 2019, advising on the risk of pregabalin abuse and dependence. Pregabalin re-classified as a Schedule 3 controlled drug. Be aware also of potential serious risks of interaction between pregabalin and other medicines that can cause CNS depression, particularly opioids.
- Pregabalin binds to the alpha-2 subunit of voltage gated calcium channels in the CNS thus inhibiting the release of excitatory neurotransmitters.
- Pregabalin has a binding affinity 6x greater than that of gabapentin.
- Oral bioavailability 90% or greater; can be taken with or without food. Peak plasma concentrations occur within 1.5 hours.

- Limited pharmacokinetic data in children suggests total exposure to pregabalin to be 30% lower in paediatric patients of weight <30kg (compared to those of weight 30kg or greater) due to increased drug clearance. Terminal half-life averaged 3-4 hours in children up to 6 years of age and 4-6 hours in those aged 7 years or older.
- Pregabalin does not bind to plasma proteins. It undergoes negligible liver metabolism nor does it affect the major CYP450 enzymes and therefore is unlikely to have significant drug interactions.
- Pregabalin is predominantly excreted unchanged by the kidneys and thus accumulates in renal impairment. Dose reduction is necessary in patients with renal impairment.
- No dosage adjustment is needed in hepatic impairment.
- Case reports of more profound psychological side effects with pregabalin than gabapentin.
- For administration via an enteral tube preferably use the oral solution. There are no specific data on the jejunal administration of pregabalin. Administer using the oral solution and monitor for loss of effect or increase in side-effects.
- Most reported adverse effects are dizziness, somnolence and headache. These are generally transient and mild to moderate in nature and may be minimised by a gradual increase to the therapeutic dose.
- Available as: oral capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg and oral solution 20 mg/ml.
- Schedule 3 controlled drug although exempt from safe storage requirements.

Evidence: [284, 337, 794-797] WRE

Promethazine

The MHRA / CHM issued advice in March 2008 and February 2009 recommending that children under the age of 6 years should not be given over the counter preparations containing promethazine. This was on the back of serious events including deaths.

Use:

- Sleep disturbance.
- Mild sedation (soporific).
- Antihistamine.
- Can also be used to treat nausea and vomiting (including motion and opioid-induced), and vertigo.
- Sedation in neonatal intensive care.

Dose and routes (for promethazine hydrochloride)
By mouth:

Symptomatic relief of allergy:

- **Child 2–4 years:** 5 mg twice daily *or* 5–15 mg at night.
- **Child 5–9 years:** 5–10 mg twice daily *or* 10–25 mg at night.
- **Child 10–17 years:** 10–20 mg 2–3 times daily *or* 25 mg at night increased to 25 mg twice daily if necessary.

Sedation (short term use):

- **Child 2–4 years:** 15-20 mg at night.
- **Child 5–9 years:** 20-25 mg at night.
- **Child 10–17 years:** 25-50 mg at night.

Nausea and vomiting (particularly in anticipation of motion sickness)

- **Child 2–4 years:** 5 mg twice daily.
- **Child 5–9 years:** 10 mg twice daily.
- **Child 10–17 years:** 20–25 mg twice daily.

Sedation in neonatal intensive care
By mouth or by slow intravenous injection

- **Neonate >37 CorGA:** 0.5–1 mg/kg 4 times daily, adjusted according to response

Notes:

- Phenothiazine antihistamine (anti H1) with moderatemuscarinic and D2 receptor antagonism. Has also been used orally for dyspnoea in adults.
- Not licensed for sedation in children under 2 years
- Used in neonatal units on bigger babies for oral sedation when usual IV sedationoptions not working. Note drug interactions, particularly causing increased antimuscarinic and sedative effects.
- Caution in epilepsy, asthma, renal and severe hepatic impairment. Risk of hypotension if co-prescribed with opioid.
- Note when prescribing, subcutaneous dose should be lower than corresponding oral dose due to significant first pass metabolism.

- Promethazine is *not* generally recommended for subcutaneous administration due to the risk of local necrosis but diluted in an adequate volume of sodium chloride 0.9% can usually be administered by CSCI over 24 hours. Do *not* give bolus SC injections.
- Oral preparation can be effective for up to 12 hours (peak plasma concentration 2-3 hours after administration). Drowsiness may wear off after a few days of treatment.
- For use by feeding tube: the elixir is slightly viscous. No further dilution is necessary, for intragastric administration, but dilute with an equal volume of water for intrajejunal administration, or to reduce viscosity and resistance to flushing. Tablets will disintegrate if shaken in water for 5 minutes.
- Available as: promethazine hydrochloride tablets (10 mg, 25 mg), oral elixir (5 mg/5 mL), and injection (25 mg/mL). (Promethazine teoclate tablets also available, 25 mg, licensed for nausea, vertigoand labyrinthine disorders. Slightly longer acting than promethazine hydrochloride and dosing slightly different).

Evidence: [338, 339, 345, 711, 798], NoRE, ARE

Ranitidine

Use:

- Gastro-oesophageal reflux oesophagitis, dyspepsia.
- Treatment of gastritis, benign gastric and duodenal ulcers.
- Gastro-protection (e.g. with combination NSAID/steroids or anticipating stress ulceration).
- Other conditions requiring reduction in gastric acid.

Dose and routes
By mouth:

- **Neonate:** 2 mg/kg 3 times daily, increasing if necessary to maximum 3 mg/kg 3 times daily (absorption unreliable).
- **Child 1–5 months:** 1 mg/kg 3 times daily increasing if necessary to maximum 3 mg/kg 3 times daily.
- **Child 6 months–2 years:** 2–4 mg/kg twice a day.
- **Child 3–11 years:** 2–4 mg/kg (maximum single dose 150 mg) twice a day. Dose may be increased up to 5 mg/kg (maximum 300 mg/dose) twice daily in severe gastro-oesophageal reflux disease,
- **Child 12–18 years:** 150 mg twice a day or 300 mg at night. May be increased if necessary, in moderate to severe gastro-oesophageal reflux disease to 300 mg twice a day or 150 mg 4 times daily for up to 12 weeks.

By slow intravenous injection, diluted to 2.5 mg/ml and given over at least 3 minutes (some adult centres give as subcutaneous injection (unlicensed route)):

- **Neonate:** 0.5–1 mg/kg every 6–8 hours (may need 2 mg/kg 8 hourly as variable first pass metabolism affects uptake).
- **Child 1 month–17 years:** 1 mg/kg (max. 50 mg) every 6–8 hours (may be given as an intermittent infusion at a rate of 25 mg/hour).

Notes:

- Oral formulations not licensed for use in children < 3 years; injection not licensed for children less than 6 months.
- Use gastric pH to judge best dose in early infancy.
- Ranitidine is an H2 antagonist.
- Proton pump inhibitors (PPIs), H2 antagonists and prokinetics all relieve symptoms of non-ulcer dyspepsia and acid reflux, PPIs being the most effective. PPIs and H2 antagonists are effective at preventing NSAID-related peptic ulcers. Adding a bedtime dose of H2 antagonist to high dose PPI may improve nocturnal acid reflux, but evidence is poor.
- Time to peak plasma concentration is 2-3 hours, half-life 2-3 hours (longer at birth and in pre-term babies), duration of action 8-12 hours.
- Ranitidine may increase plasma concentration of midazolam.
- May cause rebound hyperacidity at night.
- Via feeding tubes, use effervescent tablets as first choice, unless sodium content is a concern. Use oral liquid as alternative. (Standard tablets do not disperse readily in water).
- Can use IV if needed in severe nausea and vomiting. Some centres use subcutaneous doses BD – QDS.
- Available as: tablets and effervescent tablets (75 mg, 150 mg, 300 mg), oral solution (75 mg/5 mL NB contains ethanol) and injection (25 mg/ml).

Evidence: [337-340, 345, 799-802]

Risperidone

Use:

- Severe neuro-irritability.
- Dystonia and dystonic spasms refractory to first and second line treatment.
- Psychotic tendency / crises in Battens disease.
- Has anti-emetic activity (some experience in refractory nausea and vomiting in adults; not evaluated in children).
- Delirium.
- Treatment of mania or psychosis under specialist supervision.
- Short term treatment of persistent aggression in conduct disorder in children and in autism or moderate to severe dementia.

Dose and routes
Oral:

- **Child 5–17 years (weight 20–50 kg):** 250 micrograms once daily; increasing, if necessary, in steps of 250 microgramson alternate days to maximum of 750 micrograms daily.
- **Child 5-17 years (>50 kg):** 500 micrograms once daily; increasing in steps of 500 microgram on alternate days to maximum of 1.5 mg daily.

In Juvenile Battens Disease, may need 500 micrograms dailyincreasingto 1.5 mg TDS during crises with hallucinations: this dose can be reduced or stopped as symptoms settle (episodes usually last 1-6 weeks).

In Severe neuro-irritability, increase as below until control achieved then hold.

Day 1-2:	10 microgram/kg/day
Day 3-7:	20 microgram/kg/day
Day 8-14:	40 microgram/kg/day
Day 15-42:	60 microgram/kg/day

Notes

- Risperidone is a dopamine D2, 5-HTA, alpha-1 adrenoceptor and histamine-1 receptor antagonist.
- Risperidone is licensed for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years, using the doses above. Not licensed for use in children for mania, psychosis or autism (use different doses under specialist supervision).
- 99% bioavailable. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half-life 24 hours. Duration of action 12-48 hours.
- Caution in epilepsy (lowers seizure threshold) and cardiovascular disease; extrapyramidal symptoms less frequent than with older antipsychotic medications; can cause orthostatic hypotension; withdraw gradually after prolonged use.
- Risperidone can cause significant weight gain. Other common side effects include anxiety, depression, sleep disorders, hypertension, oedema, malaise.
- Initial and subsequent doses should be halved in renal or hepatic impairment.

- Oral liquid is the preferred preparation for administration via enteral feeding tubes. Tablets also disintegrate in water within 5 minutes for easy administration via enteral feeding tubes. There is no specific data relating to jejunal administration of risperidone. Administer using the above method. Monitor for loss of efficacy or increased side-effects. The oral liquid may be diluted in any non- alcoholic drink except tea.
- Available as: tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg), orodispersible tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg), oral solution 1 mg/mL.

Evidence: [338, 345, 539, 803-808] NoRE

Salbutamol

Use:

- Wheezing/breathlessness caused by bronchospasm including exacerbations associated with respiratory tract infection.
- Also used in hyperkalemia.
- Prevention and treatment of chronic lung disease in premature infants.
- Sometimes used in muscular disorders disorders where it is felt to have an effect on the degradation of motor neurone protein muscle weakness (seek specialist advice, not covered here).

Dose and routes for exacerbation of reversible airway obstruction, and prevention of allergen- or exercise-induced bronchospasm.

(NB see separate detailed guidance in standard texts for use in acute asthma, including for intravenous preparation, not covered here).

Aerosol inhalation:

- **Child 1 month-17 years:** 100-200 micrograms (1-2 puffs) for relief ofsymptoms up to four times a day. See separate dosing guidance for individual preparations.

Nebulised solution:

- **Neonate:** 1-2.5 mg up to four times daily,
- **Child 1 month-4 years:** 2.5 mg, then 2.5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.
- **Child 5-11 years:** 2.5-5 mg, then 2.5-5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.
- **Child 12-17 years:** 5 mg then 5 mg every 20-30minutes, or when required, give by oxygen-driven nebuliser if avaliable.

Oral liquid is available but salbutamol should generally only be admisnistered orally in the context of neuromuscular disease, where a systemic effect is felt to occur on the rate of degredation of motor neurone proteins.

Notes

- Salbutamol is a short acting beta 2 adrenergic receptor agonist.
- Salbutamol is not licensed for use in hyperkalaemia; injection is not licensed for use in children.
- In palliative care, if airflow obstruction is suspected, a pragmatic approach may be to give a trial (e.g. 1–2 weeks) of a bronchodilator and evaluate the impact on symptoms. Spirometry should normally be used to confirm a possible underlying asthma diagnosis.
- Clinical efficacy of salbutamol in infants <18 months is uncertain, presumably due to the immaturity of the receptors; ipratropium may be more helpful in those less than 1-2 years.
- For an acute episode, many paediatricians now advise multi-dosing of salbutamol 100microgram up to 10 times, via a spacer where practicable for the patient instead of a nebuliser.
- Onset of action 5 minutes inhaled; 3-5 minutes nebulised. Peak response

0.5-2 hours. Duration of action 4-6 hours. Only 10-20%of inhaled dose reaches lower airways.

- Side effects: increased heart rate; feeling “edgy” or agitated; tremor.
- The side effects listed above may prevent use, in which case ipratropium bromide is a good alternative.
- Advise family to seek advice if a previously effective dose fails to provide at least 3 hours relief and warn of the dangers of exceeding prescribed inhaler and nebuliser doses.
- Caution: tachycardia and risk of QT prolongation at increasing doses.
- Interactions: increased risk of hypokalemia with corticosteroids, diuretics, theophylline.
- Inhaled product should be used with a suitable spacer device, and the child/ carer should be given appropriate training. Inhaler technique should be explained and checked. The HFA (hydrofluoroalkane) propellant now used in multi-dose inhalers tends to clog the nozzle, so weekly cleaning is recommended.
- Salbutamol nebules are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile 0.9% NaCl. Salbutamol can be mixed with nebulised solution of ipratropium bromide.
- Available as nebuliser solution (2.5 mg in 2.5 mL, 5 mg in 2.5 mL), respirator solution (5 mg in 1 mL), aerosol inhalation (100 micrograms/puff) by metered dose inhaler (MDI), with various spacer devices. Various types of dry powder inhaler are also available, 100 and 200 microgram per puff.
  Preparations for injection (500 micrograms/ml) and intravenous infusion (1 mg/ mL) are also available.

Evidence: [337-339, 809-814]

Senna

Use:

- Constipation

Dose and routes
By mouth:
Initial doses which can be adjusted according to response and tolerance.

Syrup:

- **Child 1 month–3 years:** 2.5-10 mL of syrup once a day.
- **Child 4-17 years:** 2.5-20 mL of syrup a day.

Tablets:

- **Child 2-3 years**: 0.5-2 tablets once daily.
- **Child 4-5 years**: 0.5-4 tablets once daily.
- **Child 6-17 years**: 1-4 tablets once daily.

Notes:

- Mainly stimulant laxative acting on large bowel. Improves intestinal motility and increases water secretion into bowel lumen. Senna passes unchanged into large bowel, (therefore still effective administered into the jejunum). It is hydrolysed by bacterial flora in the large bowel to yield the active compound.
- For opioid induced constipation in palliative care a reasonable approach is to start with a stimulant alone, optimise the dose and only add a second agent if not adequately effective.
- Syrup is not licensed for use in children < 2 years and tablets are not licensed for use in children <6 years.
- Onset of action 8-12 hours.
- Initial dose should be low then increased, if necessary, often at 12-24 hour intervals.
- Doses can be exceeded on specialist advice: opioid induced constipation often requires higher doses than in manufacturer's Product Information.
- Oral liquid may be administered via an enteral feeding tube, flush well before and after the dose. Therapeutic effect will be unaffected by jejunal administration.
- Available as: tablets (7.5 mg sennoside B) and oral syrup (7.5 mg/5 mL sennoside B)
- NICE Guidance for Constipation in Children and young people advise the use of polyethylene glycol 3350 based laxatives before introducing stimulates such as senna.

Evidence: [89, 337, 338, 341, 345, 792, 815-818]

Sodium Citrate

Use:

- Constipation: Acts as osmotic laxative. Usually combined with faecal softener in micro-enemas.

Dose and routes

Micolette Micro-enema

Enema, sodium citrate 450 mg, sodium lauryl sulfoacetate 45 mg, glycerol 625 mg, together with citric acid, potassium sorbate, and sorbitol in a viscous solution, in 5-mL

- By rectum: **Child 3–17 years**: 5–10 mL as a single dose

Micralax Micro-enema

Enema, sodium citrate 450 mg, sodium alkylsulfoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL

- By rectum: **Child 3–17 years**: 5 mL as a single dose

Relaxit Micro-enema

Enema, sodium citrate 450 mg, sodium lauryl sulfate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in a 5mL single dose pack with nozzle.

- By rectum: **Child 1 month–17 years**: 5 mL as a single dose (insert only half nozzle length in child 2 years or under).

Notes

- Sodium citrate is an osmotic agent. Sodium lauryl sulfoacetate is a faecal softener.
- As micro-enema, often used in combination with oral laxatives, particularly in neuromuscular disorders, faecal loading and faecal impaction.
- Usually acts within 15 minutes of administration.
- Contraindicated in acute gastro-intestinal conditions.
- Caution: can cause harmful sodium and water retention in susceptible patients.
- Available as: micro-enema (5 mL). All currently marketed preparations include sodium citrate 90 mg/ml, but other constituents vary.
- NICE Guidance for the management of constipation in children and young people advocated 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.

Evidence: [337, 338, 792, 816-818]

Sodium Picosulfate

Use:

- Constipation (stimulant laxative).

Dose and routes:
By mouth:

- **Child 1 month–3 years:** Initial dose of 2.5 mg once a day increasing if necessary, according to response to a suggested maximum of 10 mg daily,
- **Child 4–17 years:** Initial dose of 2.5 mg once a day increasing if necessary, according to response to a suggested maximum of 20 mg daily.

Notes

- Elixir is licensed for use in children; capsules are not licensed for use in children less than 4 years of age.
- Acts as a stimulant laxative.
- 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.
- Onset of action 6-12 hours.
- Contraindicated in intestinal obstruction and dehydration.
- Effectiveness dependent upon breakdown by gut flora – previous effectiveness may therefore be lost during courses of antibiotics and ensuing altered gut flora.
- For administration via an enteral feeding tube: use the liquid preparation; dilute with an equal volume of water. Sodium picosulfate reaches the colon without any significant absorption; therefore, the therapeutic response will be unaffected by jejunal administration.
- Available as: elixir (5 mg/5 mL) and capsules (2.5 mg).

Evidence: [337, 338, 345, 792, 816-818]

Sucralfate

Use:

- Stress ulcer prophylaxis.
- Prophylaxis against bleeding from oesophageal or gastric varices; adjunct in the treatment of oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration, upper GI bleeding of unknown cause.
- Haemostasis (topical use).

Dose and route:
Oral
Stress ulcer prophylaxis. Prophylaxis against bleeding from oesophageal or gastric varices; adjunct in the treatment of: oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration, upper GI bleeding of unknown cause.

- **Child 1 month-1 year:** 250 mg four to six times daily.
- **Child 2-11 years:** 500 mg four to six times daily.
- **Child 12-14 years:** 1 g four to six times daily.
- **Child 15-17 years:** 1 g six times daily (maximum 8g/day).

Topical
For haemostasis

- Sucralfate suspension 2 g in 10 mL can be applied twice daily topically, for example as mouth wash, orally for oesophageal lesions or rectally for rectal lesions.
- Sucralfate paste can be applied topically for other lesions, made with 2 x 1g tablets crushed in 5 mL aqueous jelly lubricant such as KY jellyor water.

Notes:

- Complex of aluminium hydroxide and sulphated sucrose. In the gut it seems to act by protecting mucosa from acid-pepsin attack. Minimal antacid properties.
- Sucralfate acts locally and is minimally absorbed.
- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration.
- Spread doses evenly throughout waking hours.
- Following reports of bezoar formation associated with sucralfate, the CSM has advised caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.
- Caution – absorption of aluminium from sucralfate may be significant in patients on dialysis or with renal impairment.
- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by **at least** 1 hour to avoid formation of an insoluble complex that may block fine-bore feeding tubes. By mouth sucralfate should be given 1 hour before mealsto 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 (1 g in 5mL special order), tablets (1 g). Oral suspension, cream, powder and enema available as special order.

Evidence: [337, 338, 340, 341, 345, 819-824]

Sucrose

Use:

- Analgesia for procedural pain in babies.

Dose and routes:
By mouth:

- **Neonate >32 weeks:** 0.5-2mL of 24% sucrose orally 2 minutes before the procedure. Incremental doses 0.1mL can be used up to the maximum of 2mLs. A baby may be given multiple doses during a single procedure. Sucrose can be administered maximally up to 4 times per 24 hours in preterm infants, and up to 8 times in 24 hours in neonates and older babies.

Notes

- The effect of sucrose is enhanced when combined with other non-pharmacological techniques for providing analgesia including non-nutritive sucking and behavioural measures such as swaddling.
- Oral administration using vial dispenser directly onto the anterior portion of the tongue. If needed, the vial can be closed and laid flat after first opening and be used again in the same infant within a period of 8 hours.
- Contraindicated in babies with oesophageal atresia, trache-oesophageal fistula, confirmed or suspected intra-abdominal pathology (eg. NEC), fructose intolerance.
- Use with caution in infants with altered gag or swallow reflex / swallowing problems, cardio-respiratory instability or any major GI pathology.
- With medical approval, infants who are nil by mouth (NBM) can have the dose of oral sucrose applied with a small swab directly onto the tongue.
- Hypoglycaemia or hyperglycaemia: sucrose given orally, for procedural pain management within the recommended dosing, does not alter blood glucose levels.
- Neonates and infants of mothers maintained on methadone may have altered endogenous opiate systems, resulting in a lack of analgesic effect of oral sucrose in the first days to weeks of life.
- Endotracheal tube in situ: the NBM dose of oral sucrose may be applied directly onto the infant's tongue using a mouth swab.
- Algopedol® is licensed for use in term and preterm infants less than 4 months of age.
- Preservative-free oral solution of sucrose 24% (Algopedol®) in 2 mL vials for single patient use.

Evidence:[339, 825-829]

Tapentadol

Use:

- Opioid analgesic

Dose and Route:

Opioid naïve patient: Use the following initial doses

By mouth;

Moderate to severe acute pain (using immediate release preparations)

- **Child 2-17 years (body weight >16 kg):** 1.25 mg/kg/dose every 4 hours (maximum single dose 50 mg), 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. The maximum dose per day is 7.5mg per kg body weight (≙ 6 x single dose)(*see notes below)
- **18 years and older:** Initially 50 mg every 4–6 hours, adjusted according to response, on the first day of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose; maximum 700 mg in the first 24 hours; maximum 600 mg per day.

Severe chronic pain (using modified-release preparations)

- **18 years and older:** Initially 50 mg every 12 hours, adjusted according to response; maximum 500 mg per day.

Tapentadol is ~3x LESS potent than morphine. Oral 50 mg tapentadol = 15 mg morphine

Notes:

- Dual action centrally acting opioid analgesic; agonist at the μ-opioid receptor and inhibitor of noradrenaline reuptake. The latter enhances the action of the descending pain inhibitory pathway contributing to a synergistic analgesic effect.
- *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.
- Tapentadol can be taken with or without food.
- Tapentadol oral solution 20 mg/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.
- Tapentadol oral solution contains 2 mg/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.

- Dosage adjustment is not required in mild or moderate renal impairment. Use is not recommended in severe renal impairment.
- Dosage adjustment is not required in mild hepatic impairment. Reduce initial dose in moderate hepatic impairment. Use is not recommended in severe hepatic impairment.
- 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. The potential for drug-drug interactions is low. Plasma protein binding is low.
- Potential adverse effects as for other opioids. However GI side-effects are reportedly less than with oxycodone or morphine.
- 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.
- Care needed if switching from another μ-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).
- Available as (all Schedule 2 CD)
  - Oral solution 20 mg/mL (licensed from 2 years) Palexia®
  - Immediate-release tablets 50 mg, 75 mg (licensed from 18 years only) Palexia®
  - Modified-release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg (licensed from 18 years only) Palexia®

Evidence: [338, 340, 830-835]

Temazepam

Use:

- Sleep disturbance (short term use), especiallywhere anxiety is a cause.
- Premedication before surgery and investigations

Dose and routes
By mouth,

- **Child 12-17 years:** 10-20 mg 1hour before procedures.
- **Adult:** 10–20 mg at night. Dose may be increased to 40 mg at night in exceptional circumstances.

Notes:

- Tablets not licensed for use in children.
- Temazepam is a GABA mimetic, anxiolytic sedative.
- Oral bioavailability at least 90%; peak plasma concentration within 50 minutes of oral administration. Long plasma half life of 8-15 hours.
- Except in the imminently dying, contraindicated in respiratory depression, compromised airway and untreated sleep apnoea syndrome.
- Correct contributory factors to insomnia if possible. Use in association with non drug measures.
- Can cause paradoxical increased hostility and aggression requiring dose adjustment. Can also paradoxically increase anxiety. May impair judgement and reaction time.
- Oral solution may be administered via an enteral feeding tube. If administered via the jejunum monitor for loss of efficacy or increased side-effects.
- Available as: tablets (10 mg, 20 mg) and oral solution (10 mg/5 mL).
- Schedule 3 controlled drug (CD No register).

Evidence: [337, 338, 340, 345]

Tizanidine

Use:

- Skeletal muscle relaxant.
- Chronic severe muscle spasm or spasticity.

Dose and routes
Children doses based on WRE

- **Child 18 months–6 years:** 1 mg/day; increase if necessary, according to response.
- **Child 7-11 years:** 2 mg/day; increase if necessary, according to response.
- **Child >12 years:** as per adult dose [337]: Initially 2 mg increasing in increments of 2 mg at intervals of 3–4 days. Give total daily dose in divided doses up to 3–4 times daily. Usual total daily dose 24 mg. Maximum total daily dose 36 mg.

Children doses based on WRE

- **Child 2-15 years:** 50 microgram/kg/day in divided doses.

Notes:

- Not licensed for use in children.
- Monitor liver function monthly for first 4 months.
- Usually prescribed and titrated by neurologists.
- Timing and frequency of dosing is individual to the specific patient as maximal effect is seen after 2–3 hours and is short-lived.
- Use with caution in liver disease, monitor liver function regularly.
- Use with caution with drugs known to prolong the QT interval.
- Avoid abrupt withdrawal – risk of rebound hypertension and tachycardia.
- Tizanidine plasma concentrations are increased by CYP1A2 inhibitors potentially leading to severe hypotension.
- Drowsiness, weakness, hypotension and dry mouth are common side-effects.
- Tablets may be crushed and administered in water if preferred. May be administered via an enteral feeding tube. Tablets do not disperse readily but will disintegrate if shaken in 10 mL of water for 5 minutes. The resulting dispersion will flush via an 8Fr NG tube without blockage. There is no specific data for jejunal administration. Administer using the above method. Monitor for increased side-effects or loss of efficacy.
- Available as: tablets (2 mg, 4 mg).

Evidence: [337, 345, 372, 376, 836-841]

Tramadol

The WHO now advises there is insufficient evidence to make a recommendation for an alternative to codeine (tramadol) and recommends moving directly from non-opioids (Step 1) to low dose strong opioids for the management of moderate uncontrolled pain in children.

Use:

- Minor opioid with additional non-opioid analgesic actions.

Dose and routes
By mouth:

- **Child 5-11 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum of 4 doses in 24 hours). Increase if necessary to a maximum dose of 2 mg/kg (maximum single dose 100 mg) every 6 hours,
- **Child 12–17 years:** Initial dose of 50 mg every 4–6hours. Increase if necessary to a maximum of 400 mg/day given in divided doses every 4-6 hours.

By IM or IV injection or infusion:

- **Child 5-11 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum 4 doses in 24 hours). Increase if necessary to a maximum dose of 2 mg/kg (maximum single dose 100 mg) every 6 hours,
- **Child 12-17 years:** Initial dose of 50 mg every 4-6 hours. Dose may be increased if necessary to 100 mg every 4-6 hours. Maximum 600 mg/day in divided doses.

Notes:

- Not licensed for use in children < 12 years.
- By mouth tramadol is about 1/10 as potent as morphine.
- Onset of action after an oral dose is 30 to 60 minutes. Duration of action is 4-9hours.
- Causes less constipation and respiratory depression than the equivalent morphine dose.
- Side effects include diarrhoea, retching, fatigue and paraesthesia.
- Analgesic effect is reduced by ondansetron.
- Soluble or orodispersible tablets may be dissolved in water for administration via an enteral feeding tube or use the oral drops or disperse capsule contents. There are no specific data relating to jejunal administration, but as modified-release preparations are available it is likely that tramadol is absorbed throughout the small bowel. Administer using the above method and monitor for increased side-effects.
- Available as capsules (50 mg, 100 mg), soluble tablets (50 mg), orodispersible tablets (50 mg), m/r tablets and capsules (50 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg), oral drops (100 mg/mL) and injection (50 mg/mL). Care with prescribing as both 12-hourly and 24-hourly m/r preparations are available. Schedule 3 CD (No register Exempt Safe Custody)

Evidence: [280, 337, 338, 345, 396, 715, 842-845]

Tranexamic acid

Use:

- Oozing of blood (e.g. from mucous membranes / capillaries), particularly when due to low or dysfunctional platelets.
- Menorrhagia.

Dose and routes
By mouth:
Inhibition of fibrinolysis

- **Child 1 month–17 years:** 15–25 mg/kg (maximum 1.5 g) 2–3 times daily.

Menorrhagia

- **Child 12-17 years:** 1 g 3 times daily for up to 4 days. If very heavy bleeding a maximum daily dose of 4 g (in divided doses) may be used. Treatment should not be initiated until menstruation has started.

By intravenous injection over at least 10 minutes:

Inhibition of fibrinolysis

- **Child 1 month -17 years:** 10 mg/kg (maximum 1 g) 2-3 times a day.

By continuous intravenous infusion:

Inhibition of fibrinolysis

- **Child 1 month-17 years:** 45 mg/kg over 24 hours.

By other routes

Mouthwash 5% solution:

- **Child 6-17 years:** 5-10 mL 4 times a day for 2 days. Not to be swallowed.

Topical treatment:
Apply gauze soaked in 100mg/mL injection solution to affected area.

Notes:

- Injection not licensed for use in children under 1 year or for administration by intravenous infusion.
- Can cause clot 'colic' if used in presence of haematuria.
- Reduce dose in mild to moderate renal impairment and avoid in severe renal impairment.
- For administration via an enteral feeding tube, the oral suspension (unlicensed) or injection solution is preferred. Tablets may be dispersed in water for tube administration but may not be appropriate for small bore tubes. No specific information for jejunal administration.
- Parenteral preparation can be used topically.
- Available as: tablets (500 mg), syrup (500 mg/5 mL available from 'specials' manufacturers) and injection (100 mg/mL 5 mL ampoules). Mouthwash only as extemporaneous preparation.

Evidence: [338, 341, 846-851]

Trihexyphenidyl

Uses:

- Dystonias; Sialorrhoea (drooling); Antispasmodic.

Dose and route:
By mouth

- **Child 3 months-17 years:** Initial dose of 1-2 mg daily in 1-2 divided doses, increased every 3-7 days by 1 mg daily; adjusted according to response and side-effects; maximum 2 mg/kg/daily (maximum 70 mg/daily).

Generally, the doses needed to control drooling are much lower than those needed for dystonias.

Notes:

- Anticholinergic agent thought to act through partially blocking central (striatal) cholinergic receptors.
- Not licensed for use in children.
- Use in conjunction with careful observation and a full non-drug management programme including positioning, massage, holding, distraction, checking for causes of exacerbations etc. Advisable to seek specialist neurological input before use of trihexyphenidyl.
- Side-effects are very common and it is important to start at a low dose and increase gradually to minimise the incidence and severity. Mouth dryness, GI disturbance, blurring of vision, dizziness and nausea can occur in 30-50% patients. Less common side-effects include urinary retention, tachycardia and with very high doses CNS disturbance.
- Use with caution in children with renal or hepatic impairment.
- Onset of action is usually within 1 hour, maximum effect occurs within 2-3 hours and duration of effect ~6-12 hours.
- May take several weeks for maximal effect on dystonic movements to be seen.
- Do not withdraw abruptly in children who have been on long-term treatment.
- Tablets may be crushed and mixed in soft food.
- For administration via a gastrostomy the liquid may be used or the tablets will disperse readily in water. No specific information on jejunal administration. If this route is used monitor for any loss of efficacy or increased side-effects.
- Available as: tablets 2 mg and 5 mg; oral liquid (pink syrup) 5 mg in 5 ml.

Reference: [337, 338, 345, 531, 852-860]

Vitamin K (Phytomenadione)

Use:

- Treatment of haemorrhage associated with vitamin-K deficiency (seek specialist advice).

Dose and routes
By mouth or intravenous:

- **Neonate:** 100 micrograms/kg.
- **Child 1 month–17years**: 250-300 micrograms/kg (maximum 10 mg) as a single dose.

Notes:

- Caution with intravenous use in premature infants <2.5 kg.
- IV injections should be given very slowly – risk of vascular collapse. Dilute with Glucose 5%.
- Available as 1 mg capsules, 200 micrograms/ml oral drops and 10 mg/ml injections. Many other forms and strengths available from special order manufacturers.

Evidence:[337, 339, 341]

Appendix 1: Morphine equivalence single dose

[337, 338, 340, 725]

Analgesic	Dose
Morphine oral	10mg
Morphine subcutaneous / intravenous	5mg
Diamorphine subcutaneous / intravenous	3mg
Hydromorphone oral[1]	1.5mg
Oxycodone oral[2]	5mg
Methadone	Variable

1. Hydromorphone manufacturer recommends 2 mg however independent evidence suggests 1.5 mg preferable.
2. Oxycodone manufacturer recommends 6.6 mg however independent evidence suggests 5 mg preferable.

Appendix 2: Subcutaneous infusion drug compatibility

Evidence suggests that during end of life care in children, where the enteral route is no longer available, the majority of symptoms can be controlled by a combination of six “essential drugs” [861].

Ketamine can be used as an opioid adjuvant, on the advice of a specialist, and is useful for pain with a neuropathic component or to prevent opioid tolerance or opioid dose escalation [251].

Compatibility for these six drugs is given in the table 1 below[340].

Water for injection is usually the standard choice of diluent to minimise the likelihood of incompatibility. However, NaCl 0.9% should be considered if inflammation at the injection site occurs as long as the drug combinations are compatible[340]. For more detailed information professionals are advised to consult an appropriate reference source[346]

Table 1: Syringe driver compatibility for two drugs in water for injection [340, 346, 862, 863]

Compatible with water for injection over 24 hours								
Diamorphine								
-	Morphine sulphate							
-	-	Oxycodone*						
+	**A**	+	Midazolam					
A	+	**A**	+	Cyclizine				
A	**A**	+	+	+	Haloperidol			
+	+	+	+	**A**	-	Levomepromazine		
+	+	+	+	+	+	+	Hyoscine hydrobromide	
Compatible with NaCl 0.9% over 24 hours								
+	+	+	+	-	+	+	**No data**	Ketamine

*Data for oxycodone 10mg/mL injection. Oxycodone 50mg/mL has a differentcompatibility profile compared to the lower strength oxycodone and compatability should be considered separately and not extrapolated from one formulation to another[340].

A	Laboratory data: physically and chemically compatible in water for injection but crystallization may occur as concentrations of either drug increase
+	Compatible in water for injection at all usual concentrations (physically and/or chemically stable)
-	Combination not recommended; drugs of similar class or action

Appendix 3: Gabapentin to Pregabalin Switch for Neuropathic Pain

Gabapentin and pregabalin have similer mechanisms of action (see APPM monographs). However, gabapentin absorption is saturable, leading to non-linear pharmacokinetics**,** whereas pregabalin possesses linear pharmacokinetics. As a consequence, switching between gabapentin and pregabalin is not straight-forward and there is very limited evidence in the literature with regard to managing a switch, with no evidence in children[864].
Nonetheless, many pain centres in the UK have developed local protocols for a switch in adults,with no reports of adverse effects [865, 866]. The following conversion factors have been used:

- 1/6 is generally accepted as a standard conversion however a rangeof factors from 1/4 to 1/9 have been used to accomodate practical dosingschedules
- Lower conversion factors of 1/6 to 1/9 used for higher gabapentin dosing are to accommodate the non-linear kinetics of gabapentin

Table 2 details a switch from gabapentin to pregabalin for neuropathic pain in children extrapolated from available adult data. However, caution is requied as efficacy and safety has not been established and clinical judgment with close monitoring is required. Conversion factors used in Table 2 allows for practical dosing.

Table 2: Gabapentin to Pregabalin switch

<table>
<tr><th>Age</th><th>Gabapentin</th><th>Conversion factor</th><th>Pregabalin</th></tr>
<tr><td rowspan="3">2-11 years</td><td>5-10mg/kg BD</td><td>1/5</td><td>1-2mg/kg BD
(Max single dose 100mg BD)</td></tr>
<tr><td>5-20mg/kg TID</td><td>1/5</td><td>1.5-6mg/kg BD
(Max single dose 100mg BD)</td></tr>
<tr><td colspan="3">For conversion:
Calculate the total daily dose of gabapentin by multiplying by 2 or 3 depending on whether it is BD or TID dosing
Divide by 5 to convert to total daily dose of pregabalin
Divide by 2 to get BD dosing for pregabalin
Remember to multiply by weight</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td rowspan="3">>12 years</td><td>300mg TID</td><td>1/4.5</td><td>100mg BD</td></tr>
<tr><td>400–1200 TID</td><td>1/6 – 1/9</td><td>200mg BD</td></tr>
<tr><td colspan="3">Doses of Gabapentin above 400mg TID are capped at an equivalent of Pregabalin 200mg BD to account for the non-linear to linear pharmacokinetic switch. However, Pregabalin can be further increased on response and tolerability to a max of 300mg BD</td></tr>
</table>

Conversion for < 2 years is not provided as the APPM does not currently have evidence for the use of pregabalin in this age group (see pregabalin monograph).

Switching from Gabapentin to Pregabalin for seizure control is outside the scope of the APPM, however manufacturers do advise that doses should be tapered rather than switching directly. Seek advice from neurologists.

Appendix 4: Benzodiazepines

(1) Approximate equivalent oral anxiolytic-sedative doses [1,2]

Benzodiazepine	Dose
Clobazam	10mg[1,2]
Clonazepam	250micrograms[1,2]
Diazepam	5mg[1,2]
Lorazepam	500micrograms[1,2]
Midazolam	5mg[2]
Nitrazepam	5mg[1,2]

(2) Comparative pharmacokinetic data.

Diazepam

[2]	Bioavailability	Onset of action (mins)	Time to peak plasma concentration (mins)	Duration of action (hrs)	Half-life (hrs) (including active metabolites)
Diazepam oral	>90%[2]	15-30[3] 30-90 [2]	30-90[2]	3-30[2]	25-50[2] 20-100[3]
Diazepam IV		1-5[2]	≤15 (oil)[2] ≥15 (emulsion)[2]	15-60[2]	
Diazepam PR	65-85%[2] 90%	<30[2]	10-30mins <30[2]		

*Metabolism and elimination in the neonate are markedly slower than in children.The half-life of diazepam is reduced in younger adults and children (approximately 18 hours)

Lorazepam

[2]	Bioavailability	Onset of action (mins)	Time to peak plasma concentration (mins)	Duration of action (hrs)	Half-life (hrs) (including active metabolites)
Lorazepam SL		5[2]	150[2]		
Lorazepam oral	90%[2,3]	10-15[2]	150[2] 120[3]	6-72 8[3]	10-20[2,3]
Lorazepam IV		2-5[3] 10		4-6[3]	12-16

Midazolam

[2. 3]	Bioavailability	Onset of action (mins)	Time to peak plasma concentration (mins)	Duration of action (hrs)	Half-life (hrs) (including active metabolites)
Midazolam buccal	85%[2]	15[2] 5[3]	≤30[2]		
Midazolam oral	40%[2]	20-30 10-30[3]	30-60[2]	<4[2] 20-90mins[3]	1-4 [2] 2-5 [2,3]
Midazolam SC	95%[2]	5-10[2]	30[2]		
Midazolam IV		2-3[2,3]		30-60mins[3]	

References:

1. = [337]
2. = [340]
3. = [341]

Appendix 5: 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 2nd 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 3rd Edition

Different to 2nd 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

rainbows
hospice for children and young people

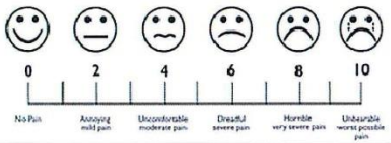
SYRINGE DRIVER PRESCRIPTION AND CHECK LIST

Name: _____ **Date of Birth:** _____ **Syringe size:** _____

Syringe Driver serial number: _____ **Total Volume:** _____

Date	Time Started	Medication	Dose Over 24 hrs	Batch No	DRs Signature	Checked	
		Dilutent:					

Time																								
Rate: ml/hr																								
Amount infused																								
Site check																								
Respiration rate																								
Pain assessment																								
PRN medication																								
Sedative effect																								
Suctioning																								
Position change																								
Connection check																								
Signature/Initial																								

Pain	Sedative Effects	Site Check		Amount of Medication Discarded
	Awake/settled – 1 Semi-conscious state – 2 Restless/Unsettled – 3 Anxious/Agitated – 4 Asleep – 5 Unresponsive – 6	Clean/no redness Redness/no warmth Tracking/warm Blood/inflammation Infiltration	= 1 = 2 = 3 = 4 = 5	..... ml Date ..... Time ..... Signed ..... Signed .....

Updated 2019

References

1. Davis, M.P., et al., *Appetite and cancer-associated anorexia: a review.* J Clin Oncol, 2004. **22**(8): p. 1510-7.
2. Duval, M. and C. Wood, *[Treatment of non-painful symptoms in terminally ill children].* Arch Pediatr, 2002. **9**(11): p. 1173-8.
3. Goldman, A., et al., *Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/Paediatric Oncology Nurses Forum survey.* Pediatrics, 2006. **117**(6): p. e1179-86.
4. Peng, J.K., et al., *What can family physicians contribute in palliative home care in Taiwan?* Fam Pract, 2009. **26**(4): p. 287-93.
5. Santucci, G. and J.W. Mack, *Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting, constipation, anorexia, cachexia.* Pediatr Clin North Am, 2007. **54**(5): p. 673-89, x.
6. Theunissen, J.M., et al., *Symptoms in the palliative phase of children with cancer.* Pediatr Blood Cancer, 2007. **49**(2): p. 160-5.
7. Walsh, D., S. Donnelly, and L. Rybicki, *The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients.* Support Care Cancer, 2000. **8**(3): p. 175-9.
8. Wolfe, J., et al., *Symptoms and suffering at the end of life in children with cancer.* N Engl J Med, 2000. **342**(5): p. 326-33.
9. Durant, P.A. and T.L. Yaksh, *Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats.* Anesthesiology, 1988. **68**(3): p. 325-34.
10. Awqati, N.A., et al., *Causes and differentials of childhood mortality in Iraq.* BMC Pediatr, 2009. **9**(1): p. 40.
11. Cash, S. and A. Shinnick-Page, *Basic life support and children with profound and multiple learning disabilities.* Paediatr Nurs, 2008. **20**(8): p. 38-9.
12. Chang, A.B., et al., *Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults.* Cochrane Database Syst Rev, 2005(2): p. CD004823.
13. Collins, J.J., et al., *The measurement of symptoms in children with cancer.* J Pain Symptom Manage, 2000. **19**(5): p. 363-77.
14. de Groot, I.J. and L.P. de Witte, *Physical complaints in ageing persons with spinal muscular atrophy.* J Rehabil Med, 2005. **37**(4): p. 258-62.
15. Fogarasi, A., J. Janszky, and I. Tuxhorn, *Autonomic symptoms during childhood partial epileptic seizures.* Epilepsia, 2006. **47**(3): p. 584-8.
16. Hanayama, K., et al., *Dysphagia in patients with Duchenne muscular dystrophy evaluated with a questionnaire and videofluorography.* Disabil Rehabil, 2008. **30**(7): p. 517-22.
17. Kravitz, R.M., *Airway clearance in Duchenne muscular dystrophy.* Pediatrics, 2009. **123 Suppl 4**: p. S231-5.
18. Laub, M., S. Berg, and B. Midgren, *Symptoms, clinical and physiological findings motivating home mechanical ventilation in patients with neuromuscular diseases.* J Rehabil Med, 2006. **38**(4): p. 250-4.
19. Miske, L.J., et al., *Use of the mechanical in-exsufflator in pediatric patients with neuromuscular disease and impaired cough.* Chest, 2004. **125**(4): p. 1406-12.
20. Simonds, A.K., *Recent advances in respiratory care for neuromuscular disease.* Chest, 2006. **130**(6): p. 1879-86.

21. Zylicz, Z. and M. Krajnik, *The use of antitussive drugs in terminally ill patients.* European Journal of Palliative Care, 2004. **11**(6): p. 225-9.
22. Baumann, F., et al., *Clinical Characteristics of the End-of-Life Phase in Children with Life-Limiting Diseases: Retrospective Study from a Single Center for Pediatric Palliative Care.* Children (Basel), 2021. **8**(6).
23. Bellomo-Brandao, M.A., E.F. Collares, and E.A. da-Costa-Pinto, *Use of erythromycin for the treatment of severe chronic constipation in children.* Braz J Med Biol Res, 2003. **36**(10): p. 1391-6.
24. Bromley, D., *Abdominal massage in the management of chronic constipation for children with disability.* Community Pract, 2014. **87**(12): p. 25-9.
25. Candy, D.C., D. Edwards, and M. Geraint, *Treatment of faecal impaction with polyethelene glycol plus electrolytes (PGE + E) followed by a double-blind comparison of PEG + E versus lactulose as maintenance therapy.* J Pediatr Gastroenterol Nutr, 2006. **43**(1): p. 65-70.
26. Clark, K., et al., *Assessing the Presence and Severity of Constipation with Plain Radiographs in Constipated Palliative Care Patients.* J Palliat Med, 2016. **19**(6): p. 617-21.
27. Flerlage, J.E. and J.N. Baker, *Methylnaltrexone for Opioid-Induced Constipation in Children and Adolescents and Young Adults with Progressive Incurable Cancer at the End of Life.* J Palliat Med, 2015. **18**(7): p. 631-3.
28. Hauch, H., et al., *Gastrointestinal Symptoms in Children With Life-Limiting Conditions Receiving Palliative Home Care.* Front Pediatr, 2021. **9**: p. 654531.
29. Hauer, J., *Feeding Intolerance in Children with Severe Impairment of the Central Nervous System: Strategies for Treatment and Prevention.* Children (Basel), 2017. **5**(1).
30. Steele, R., et al., *Charting the territory: symptoms and functional assessment in children with progressive, non-curable conditions.* Arch Dis Child, 2014. **99**(8): p. 754-62.
31. Johnson, L.M., et al., *An unusual case of Ogilvie syndrome in a pediatric oncology patient receiving palliative care after failed treatment with neostigmine.* J Palliat Med, 2012. **15**(9): p. 1042-6.
32. Lemaire, A., et al., *Effectiveness of naloxegol in patients with cancer pain suffering from opioid-induced constipation.* Support Care Cancer, 2021. **29**(12): p. 7577-7586.
33. Lin, A.J., et al., *Improved Bowel Function With Oral Methylnaltrexone Following Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis.* J Pediatr Orthop, 2021.
34. NICE guidance. *Constipation in Children and Young People: diagnosis and management.* . 2017; CG99 [Available from: http://guidance.nice.org.uk/CG99.
35. Novak, C., et al., *Peripherally acting mu-opioid receptor antagonists for treatment of opioid-induced constipation in children.* Paediatr Child Health, 2021. **26**(2): p. e105-e109.
36. Thomson, M.A., et al., *Polyethylene glycol 3350 plus electrolytes for chronic constipation in children: a double blind, placebo controlled, crossover study.* Arch Dis Child, 2007. **92**(11): p. 996-1000.
37. Wolfe, J., et al., *Symptoms and suffering at the end of life in children with cancer.* New England Journal of Medicine, 2000. **342**(5): p. 326-333.
38. Vijayvargiya, P., et al., *Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation.* Aliment Pharmacol Ther, 2020. **52**(1): p. 37-53.
39. Zernikow, B., E. Michel, and B. Anderson, *Transdermal fentanyl in childhood and adolescence: a comprehensive literature review.* J Pain, 2007. **8**(3): p. 187-207.
40. Awasthi, S. and I.C.Z.E.f.D. Group, *Zinc supplementation in acute diarrhea is acceptable, does not interfere with oral rehydration, and reduces the use of other medications: a randomized trial in five countries.* J Pediatr Gastroenterol Nutr, 2006. **42**(3): p. 300-5.

41. CaJacob, N.J. and M.B. Cohen, *Update on Diarrhea.* Pediatr Rev, 2016. **37**(8): p. 313-22.
42. do Carmo, M.S., et al., *Probiotics, mechanisms of action, and clinical perspectives for diarrhea management in children.* Food Funct, 2018. **9**(10): p. 5074-5095.
43. Fischer Walker, C., et al., *Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials.* Am J Clin Nutr, 2005. **82**(1): p. 5-12.
44. Guarino, A., A. Lo Vecchio, and R. Berni Canani, *Chronic diarrhoea in children.* Best Pract Res Clin Gastroenterol, 2012. **26**(5): p. 649-61.
45. Heyman, M.B., et al., *Fruit Juice in Infants, Children, and Adolescents: Current Recommendations.* Pediatrics, 2017. **139**(6).
46. Montgomery, K.E., et al., *Comparison of child self-report and parent proxy-report of symptoms: Results from a longitudinal symptom assessment study of children with advanced cancer.* J Spec Pediatr Nurs, 2021. **26**(3): p. e12316.
47. Mottacki, N., M. Simren, and A. Bajor, *Review article: bile acid diarrhoea - pathogenesis, diagnosis and management.* Aliment Pharmacol Ther, 2016. **43**(8): p. 884-898.
48. Ofei, S.Y. and G.J. Fuchs, 3rd, *Principles and Practice of Oral Rehydration.* Curr Gastroenterol Rep, 2019. **21**(12): p. 67.
49. Shankar, A.H. and A.S. Prasad, *Zinc and immune function: the biological basis of altered resistance to infection.* Am J Clin Nutr, 1998. **68**(2 Suppl): p. 447S-463S.
50. Szajewska, H., et al., *Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children.* J Pediatr Gastroenterol Nutr, 2016. **62**(3): p. 495-506.
51. Szajewska, H. and M. Kolodziej, *Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea.* Aliment Pharmacol Ther, 2015. **42**(7): p. 793-801.
52. Craig, F., E.M. Henderson, and M. Bluebond-Langner, *Management of respiratory symptoms in paediatric palliative care.* Curr Opin Support Palliat Care, 2015. **9**(3): p. 217-26.
53. Galbraith, S., et al., *Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial.* J Pain Symptom Manage, 2010. **39**(5): p. 831-8.
54. Hardinge, M., et al., *British Thoracic Society guidelines for home oxygen use in adults.* Thorax, 2015. **70 Suppl 1**: p. i1-43.
55. Hardinge, M., et al., *Guideline update: The British Thoracic Society Guidelines on home oxygen use in adults.* Thorax, 2015. **70**(6): p. 589-91.
56. Barnes, H., et al., *Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness.* Cochrane Database Syst Rev, 2016. **3**: p. CD011008.
57. Simon, S.T., et al., *Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults.* Cochrane Database Syst Rev, 2016. **10**: p. CD007354.
58. Navigante, A.H., et al., *Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer.* J Pain Symptom Manage, 2006. **31**(1): p. 38-47.
59. Camfield, P.R., *Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial.* J Pediatr, 1999. **135**(3): p. 398-9.
60. Filin, A., S. Treisman, and A. Peles Bortz, *Radiation therapy preparation by a multidisciplinary team for childhood cancer patients aged 31/2 to 6 years.* J Pediatr Oncol Nurs, 2009. **26**(2): p. 81-5.
61. Holmes, G.L. and J.J. Riviello, Jr., *Midazolam and pentobarbital for refractory status epilepticus.* Pediatr Neurol, 1999. **20**(4): p. 259-64.
62. Jennings, P.D., *Providing pediatric palliative care through a pediatric supportive care team.* Pediatr Nurs, 2005. **31**(3): p. 195-200.

63. Mitchell, W.G., *Status epilepticus and acute repetitive seizures in children, adolescents, and young adults: etiology, outcome, and treatment.* Epilepsia, 1996. **37 Suppl 1**: p. S74-80.
64. Mpimbaza, A., et al., *Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial.* Pediatrics, 2008. **121**(1): p. e58-64.
65. O'Dell, C., et al., *Emergency management of seizures in the school setting.* J Sch Nurs, 2007. **23**(3): p. 158-65.
66. Quest, T.E., C.A. Marco, and A.R. Derse, *Hospice and Palliative Medicine: New Subspecialty, New Opportunities.* Ann Emerg Med, 2009.
67. Vats, T.S. and P.D. Reynolds, *Pediatric hospital dying trajectories: what we learned and can share.* Pediatr Nurs, 2006. **32**(4): p. 386-92.
68. Weissman, D.E., *Decision making at a time of crisis near the end of life.* Jama, 2004. **292**(14): p. 1738-43.
69. Ann Goldman, R.H., Stephen Liben,, *Oxford Textbook of Palliative Care for Children*. 2012: Oxford University Press.
70. Mannix K. , *With the end in mind: how to live and die well*. 2018, London: William Collins.
71. Broden, E.G., et al., *Defining a "Good Death" in the Pediatric Intensive Care Unit.* Am J Crit Care, 2020. **29**(2): p. 111-121.
72. Twycross RG. , *Introducing palliative care.* 4th ed. 2003, Abingdon:: Radcliffe Medical Press.
73. NICE, *End of life care for infants, children and young people with life-limiting conditions: planning and management*, NICE, Editor 2019: London.
74. Beecham, E., et al., *Keeping all options open: Parents' approaches to advance care planning.* Health Expect, 2017. **20**(4): p. 675-684.
75. Brouwer, M.A., et al., *Breaking bad news: what parents would like you to know.* Arch Dis Child, 2021. **106**(3): p. 276-281.
76. Drake, R., J. Frost, and J.J. Collins, *The symptoms of dying children.* J Pain Symptom Manage, 2003. **26**(1): p. 594-603.
77. Dussel, V., et al., *Looking beyond where children die: determinants and effects of planning a child's location of death.* J Pain Symptom Manage, 2009. **37**(1): p. 33-43.
78. Bluebond-Langner, M., et al., *Problems with preference and place of death for children too.* BMJ, 2015. **351**: p. h6123.
79. Gibson-Smith, D., S.W. Jarvis, and L.K. Fraser, *Place of death of children and young adults with a life-limiting condition in England: a retrospective cohort study.* Arch Dis Child, 2020.
80. Baile, W.F., et al., *SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer.* Oncologist, 2000. **5**(4): p. 302-11.
81. Aldridge, J., et al., *'I can't tell my child they are dying'. Helping parents have conversations with their child.* Arch Dis Child Educ Pract Ed, 2017. **102**(4): p. 182-187.
82. Boles, J.C. and M.T. Jones, *Legacy perceptions and interventions for adults and children receiving palliative care: A systematic review.* Palliat Med, 2021. **35**(3): p. 529-551.
83. McCulloch, R., et al., *Use of buccal morphine in the management of pain in children with life-limiting conditions: Results of a laboratory study.* Palliat Med, 2018. **32**(2): p. 554-558.
84. Jeon, Y.S., A.M. Kearney, and P.G. Baker, *Management of hiccups in palliative care patients.* BMJ Support Palliat Care, 2018. **8**(1): p. 1-6.
85. Bais, J.E., et al., *Surgical treatment for recurrent gastro-oesophageal reflux disease after failed antireflux surgery.* Br J Surg, 2000. **87**(2): p. 243-249X.
86. Button, B.M., et al., *Chest physiotherapy, gastro-oesophageal reflux, and arousal in infants with cystic fibrosis.* Arch. Dis. Child., 2004. **89**(5): p. 435-439.

87. Ceriati, E., et al., *Surgery in disabled children: general gastroenterological aspects.* Acta Paediatr Suppl, 2006. **95**(452): p. 34-7.
88. Craig, W.R., et al., *Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years.* The Cochrane Database of Systematic Reviews, 2004. **2004**(3.).
89. Demol, P., H.J. Ruoff, and T.R. Weihrauch, *Rational pharmacotherapy of gastrointestinal motility disorders.* Eur J Pediatr, 1989. **148**(6): p. 489-95.
90. Gold, B.D., *Review article: epidemiology and management of gastro-oesophageal reflux in children.* Aliment Pharmacol Ther, 2004. **19 Suppl 1**: p. 22-7.
91. Keady, S., *Update on drugs for gastro-oesophageal reflux disease.* Arch Dis Child Educ Pract Ed, 2007. **92**(4): p. ep114-8.
92. Lehwald, N., et al., *Sandifer syndrome--a multidisciplinary diagnostic and therapeutic challenge.* Eur J Pediatr Surg, 2007. **17**(3): p. 203-6.
93. Pritchard, D.S., N. Baber, and T. Stephenson, *Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old.* Br J Clin Pharmacol, 2005. **59**(6): p. 725-9.
94. Salvatore, S., B. Hauser, and Y. Vandenplas, *The natural course of gastro-oesophageal reflux.* Acta Paediatr, 2004. **93**(8): p. 1063-9.
95. Salvatore, S. and Y. Vandenplas, *Gastro-oesophageal reflux disease and motility disorders.* Best Pract Res Clin Gastroenterol, 2003. **17**(2): p. 163-79.
96. Tolia, V. and Y. Vandenplas, *Systematic review: the extra-oesophageal symptoms of gastro-oesophageal reflux disease in children.* Aliment Pharmacol Ther, 2009. **29**(3): p. 258-72.
97. Beckwith, R.A., *Nursing responsibilities to percutaneous endoscopic gastrostomy patients.* Gastroenterol Nurs, 2009. **32**(2): p. 127.
98. Brant, C.Q., P. Stanich, and A.P. Ferrari, Jr., *Improvement of children's nutritional status after enteral feeding by PEG: an interim report.* Gastrointest Endosc, 1999. **50**(2): p. 183-8.
99. Burd, A. and R.S. Burd, *Guide for home gastrostomy tube care.* Adv Neonatal Care, 2003. **3**(4): p. 206-7.
100. Craig, G.M. and G. Scambler, *Negotiating mothering against the odds: gastrostomy tube feeding, stigma, governmentality and disabled children.* Soc Sci Med, 2006. **62**(5): p. 1115-25.
101. Hazel, R., *The psychosocial impact on parents of tube feeding their child.* Paediatr Nurs, 2006. **18**(4): p. 19-22.
102. Hirsch, B.Z., *Nutrition via gastrostomy tube in children with cancer.* J Pediatr, 1996. **128**(1): p. 164.
103. Marin, O.E., et al., *Safety and efficacy of percutaneous endoscopic gastrostomy in children.* Am J Gastroenterol, 1994. **89**(3): p. 357-61.
104. Mathus-Vliegen, L.M. and H. Koning, *Percutaneous endoscopic gastrostomy and gastrojejunostomy: a critical reappraisal of patient selection, tube function and the feasibility of nutritional support during extended follow-up.* Gastrointest Endosc, 1999. **50**(6): p. 746-54.
105. Puntis, J.W., *Nutritional support at home and in the community.* Arch Dis Child, 2001. **84**(4): p. 295-8.
106. Reading, R., *Gastrostomy tube feeding in children with cerebral palsy: a prospective, longitudinal study.* Child: Care, Health and Development, 2005. **31**(4): p. 491-492.
107. Samuel, M. and K. Holmes, *Quantitative and qualitative analysis of gastroesophageal reflux after percutaneous endoscopic gastrostomy.* J Pediatr Surg, 2002. **37**(2): p. 256-61.

108. Sullivan, P.B., et al., *Impact of gastrostomy tube feeding on the quality of life of carers of children with cerebral palsy.* Dev Med Child Neurol, 2004. **46**(12): p. 796-800.
109. Sullivan, P.B., et al., *Prevalence and severity of feeding and nutritional problems in children with neurological impairment: Oxford Feeding Study.* Dev Med Child Neurol, 2000. **42**(10): p. 674-80.
110. Tilton, A.H., M.D. Miller, and V. Khoshoo, *Nutrition and swallowing in pediatric neuromuscular patients.* Semin Pediatr Neurol, 1998. **5**(2): p. 106-15.
111. Anderson, A.K., et al., *Artificial nutrition and hydration for children and young people towards end of life: consensus guidelines across four specialist paediatric palliative care centres.* BMJ Support Palliat Care, 2021. **11**(1): p. 92-100.
112. Breaks, A., et al., *Blended diets for gastrostomy fed children and young people: a scoping review.* J Hum Nutr Diet, 2018. **31**(5): p. 634-646.
113. Brown, S., *Blended food for enteral feeding via a gastrostomy.* Nurs Child Young People, 2014. **26**(9): p. 16-20.
114. Coad, J., et al., *Blended foods for tube-fed children: a safe and realistic option? A rapid review of the evidence.* Arch Dis Child, 2017. **102**(3): p. 274-278.
115. Craig, G.M., *Psychosocial aspects of feeding children with neurodisability.* Eur J Clin Nutr, 2013. **67 Suppl 2**: p. S17-20.
116. Enteral Plastic Safety Group/BDA, *Liquidised food statement*, 2016: https://www.peng.org.uk/pdfs/hcp-resources/enteral-plastic-safety-groupstatement.pdf.
117. Lapwood S, B.S., Griffith R, Kennedy A, Lewis J,, *Use of blended / liquidised 'table food' diets via gastrostomy: Questions and Answers* 2017: https://www.togetherforshortlives.org.uk/resource/use-of-liquidised-table-food-diets-via-gastrostomy-qa/.
118. Pentiuk, S., et al., *Pureed by gastrostomy tube diet improves gagging and retching in children with fundoplication.* JPEN J Parenter Enteral Nutr, 2011. **35**(3): p. 375-9.
119. OxSTAR, *Video resources to support gastrostomy and blended diet*: https://www.oxstar.ox.ac.uk/more/supporting-parents/watch-the-videos
120. Thomas, S., *Multi-agency practice for developing a blended diet for children fed via gastrostomy.* Nurs Child Young People, 2017. **29**(6): p. 22-25.
121. Aadhaar O'Gorman, E., *Complete Tubefeeding: Everything you need to know about tubefeeding, tube nutrition, and blended diets* 2012: CreateSpace Independent Publishing Platform
122. Leicestershire Partnership NHS Trust, *Administration of liquidised diet via gastrostomy device* 2020: https://www.leicspart.nhs.uk/wp-content/uploads/2020/05/Administration-of-Blended-Diet-via-gastrostomy-device-exp-May-22.pdf
123. Oxford Health Foundation Trust, *Procedural Guidance for the Administration of Blended Diet*, 2020.
124. Phillips G, *Patient and carer experience of blended diet via gastrostomy: a qualitative study. .* Journal of Human Nutrition and Dietetics, 2019. **32**(3): p. 391-399.
125. British Dietetic Association, *The Use of Blended Diet with Enteral Feeding Tubes*, 2021: https://www.bda.uk.com/resource/launch-of-bda-practice-toolkit-the-use-of-blended-diet-with-enteral-feeding-tubes.html
126. British Dietetic Association, *Practice Toolkit Liquidised Food via Gastrostomy Tube*, 2021: 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.
127. Connor S, *Global Atlas of Palliative Care*. 2nd ed, ed. C. S. 2020, London: WHPCA.

128. Amery J. Sengooba J. Kasirye I. Meiring M, *Chapter 12: HIV/AIDS*, in *Children's Palliative Care in Africa*, J. Amery, Editor. 2009, Oxford University Press: Oxford. p. 207-226.
129. Amery J, *Section 2: Symptom control in children's palliative care*, in *Children's Palliative Care in Africa*, Amery J, Editor. 2009, Oxford University Press: Oxford. p. 95-96.
130. UNAIDS *UNAIDS Data 2021*. 2021.
131. UNICEF, *HIV and AIDS Sub-Saharan Snapshot. Pregnant Women, Children and Adolescents. November 2021*, UNICEF, Editor 2021, UNICEF: http://www.childrenandaids.org/sites/default/files/2021-11/2021%20Sub-Saharan%20Africa%20HIV%20Snapshot%20Children%20and%20Adolescents.pdf.
132. Meiring M and Arscott-Mills T, *Palliative care for children with communicable illnesses*, in *Oxford Textbook of Palliative Care for Children (3rd edition)*, G.A. Hain R, Rapoport A and Meiring M (Eds), Editor. 2021, Oxford University Press: Oxford.
133. Stein, A., et al., *Communication with children and adolescents about the diagnosis of their own life-threatening condition.* Lancet, 2019. **393**(10176): p. 1150-1163.
134. Dalton, L., et al., *Communication with children and adolescents about the diagnosis of a life-threatening condition in their parent.* Lancet, 2019. **393**(10176): p. 1164-1176.
135. Lavy, V., *Presenting symptoms and signs in children referred for palliative care in Malawi.* Palliat Med, 2007. **21**(4): p. 333-9.
136. UNICEF, *UNICEF 2021 World AIDS Day Report. Stolen Childhood, Lost Adolescence* Uno5439956/Schermbrucker, Editor 2021, UNICEF.
137. WHO, *Consolidated Guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a Public Health Approach*, WHO, Editor 2021, WHO Geneva: https://www.who.int/publications/i/item/9789240031593.
138. Schmidt, P., et al., *Multidrug-resistant bacteria in a paediatric palliative care inpatient unit: results of a one year surveillance.* GMS Hyg Infect Control, 2020. **15**: p. Doc03.
139. Barclay, A.R., et al., *The continued rise of paediatric home parenteral nutrition use: Implications for service and the improvement of longitudinal data collection.* Clin Nutr, 2015. **34**(6): p. 1128-32.
140. Hauer. J., *Feeding Intolerance in Children with Severe Impairment of the Central Nervous System: Strategies for Treatment and Prevention. .* Children 2018. **5**(1).
141. Hauer, J., et al., *Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System.* Pediatrics, 2017. **139**(6).
142. Romano, C., et al., *European Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Neurological Impairment.* J Pediatr Gastroenterol Nutr, 2017. **65**(2): p. 242-264.
143. Richards, C.A., *Does retching matter? Reviewing the evidence-Physiology and forces.* J Pediatr Surg, 2019. **54**(4): p. 750-759.
144. Twamley, K., et al., *Underlying barriers to referral to paediatric palliative care services: knowledge and attitudes of health care professionals in a paediatric tertiary care centre in the United Kingdom.* J Child Health Care, 2014. **18**(1): p. 19-30.
145. Lotz, J.D., et al., *"Hope for the best, prepare for the worst": A qualitative interview study on parents' needs and fears in pediatric advance care planning.* Palliat Med, 2017. **31**(8): p. 764-771.
146. Lotz, J.D., et al., *Pediatric advance care planning from the perspective of health care professionals: a qualitative interview study.* Palliat Med, 2015. **29**(3): p. 212-22.

147. Lotz, J.D., et al., *Pediatric advance care planning: a systematic review.* Pediatrics, 2013. **131**(3): p. e873-80.
148. Warlow, T.A. and R.D.W. Hain, *'Total Pain' in Children with Severe Neurological Impairment.* Children (Basel), 2018. **5**(1).
149. Box, D., *Systematic Review of Paediatric Advanced Care Planning. Barriers to Implementation*, 2017: Association of Paediatric Palliative Medicine Study Day.
150. Chen, C.F., et al., *Assessment of chemotherapy-induced oral complications in children with cancer.* J Pediatr Oncol Nurs, 2004. **21**(1): p. 33-9.
151. Botteron, S., et al., *Orofacial dysfunction in Duchenne muscular dystrophy.* Arch Oral Biol, 2009. **54**(1): p. 26-31.
152. Coulson, S., *Mouth care in children with cancer.* Paediatr Nurs, 2007. **19**(4): p. 18.
153. Gibson, F., *Best practice in oral care for children and young people being treated for cancer: can we achieve consensus?* Eur J Cancer, 2004. **40**(8): p. 1109-10.
154. Williams, P.D., et al., *Symptom monitoring and dependent care during cancer treatment in children: pilot study.* Cancer Nurs, 2006. **29**(3): p. 188-97.
155. Schiffman, S.S., *Influence of medications on taste and smell.* World J Otorhinolaryngol Head Neck Surg, 2018. **4**(1): p. 84-91.
156. Fairhurst, C.B. and H. Cockerill, *Management of drooling in children.* Arch Dis Child Educ Pract Ed, 2011. **96**(1): p. 25-30.
157. NICE evidence summary ES5, *Severe sialorrhoea (drooling) in children and young people with chronic neurological disorders: oral glycopyrronium bromide*, NICE, Editor 2017, NICE: https://www.nice.org.uk/advice/es5/resources.
158. NICE guidline NG62, *Cerebral palsy in under 25s: assessment and management*, NICE, Editor 2017, NICE: https://www.nice.org.uk/guidance/ng62.
159. NICE scenario, *Treatment of oral candida in children*, NICE, Editor 2021, NICE: https://cks.nice.org.uk/topics/candida-oral/management/children-not-immunocompromised/.
160. CCLG, *Mouthcare for Children & Young People with Cancer. Children's Cancer & Leukaemia Group (CCLG) Evidence Based Guidelines*, 2005: https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/Mouth_Care_at_a_Glance.pdf.
161. BNFc, *British National Formulary for Children*, 2021, NICE: https://bnfc.nice.org.uk/.
162. Luscombe, M.D., B.D. Owens, and D. Burke, *Weight estimation in paediatrics: a comparison of the APLS formula and the formula 'Weight=3(age)+7'.* Emerg Med J.
163. Varghese, A., et al., *Do the length-based (Broselow) Tape, APLS, Argall and Nelson's formulae accurately estimate weight of Indian children?* Indian Pediatr, 2006. **43**(10): p. 889-94.
164. APLS, *The Pediatric Emergency Medicine Resource*. 4th ed.: Jones and Bartlett Publishers.
165. Rusalen, F., et al., *Perinatal palliative care: a dedicated care pathway.* BMJ Support Palliat Care, 2021. **11**(3): p. 329-334.
166. Lago, P., et al., *Summary of the Key Concepts on How to Develop a Perinatal Palliative Care Program.* Front Pediatr, 2020. **8**: p. 596744.
167. Cortezzo, D.E., K. Bowers, and M. Cameron Meyer, *Birth Planning in Uncertain or Life-Limiting Fetal Diagnoses: Perspectives of Physicians and Parents.* J Palliat Med, 2019. **22**(11): p. 1337-1345.
168. British, A., of, Perinatal, Medicine., *Palliative care - a framework for clinical practice in perinatal medicine*, 2010, BAPM: https://www.bapm.org/resources/30-palliative-care-a-framework-for-clinical-practice-in-perinatal-medicine-2010.

169. Together, f., Short, Lives. , *A perinatal pathway for babies with palliative care needs.* , T.f.S. Lives, Editor 2017: https://www.togetherforshortlives.org.uk/resource/perinatal-pathway-babies-palliative-care-needs
170. APPM, *Association of Pediatric Palliative Medicine Master Formulary 2020 Edition 5*, S. Jassal, Editor 2020, Together for Short Lives: https://www.appm.org.uk/_webedit/uploaded-files/All%20Files/Event%20Resources/2020%20APPM%20Master%20Formulary%202020%20protected.pdf.
171. Gossling, L., et al., *Investigating and managing neonatal seizures in the UK: an explanatory sequential mixed methods approach.* BMC Pediatr, 2020. **20**(1): p. 36.
172. Hart AR, P.E., Alix JJP *Neonatal seizures—part 2: Aetiology of acute symptomatic seizures, treatments and the neonatal epilepsy syndromes*. Archives of Disease in Childhood - Education and Practice 2015. **100**, 226-232.
173. British Association of Perinatal Medicine, *Therapeutic hypothermia for neonatal encephalopathy: A BAPM framework for practice*, 2020, BAPM: https://hubble-liveassets.s3.amazonaws.com/bapm/attachment/file/399/TH_document_for_publication.pdf.
174. Jackson C. Vasudevan C., *Palliative care in the neonatal intensive care unit.* Paediatrics and Child Health, 2020. **30**(4): p. 124-128.
175. Chelsea and Westminster Hospital NHS Foundation Trust and Royal College of Paediatrics and Child Health (RCPCH), *Practical guidance for the management of palliative care on neonatal units*, 2014, Chelsea and Westminster Hospital NHS Foundation Trust: https://www.chelwest.nhs.uk/services/childrens-services/neonatal-services/links/Practical-guidance-for-the-management-of-palliative-care-on-neonatal-units-Feb-2014.pdf.
176. Boyle, E., *Management of pain in the neonatal unit: options, challenges and controversies.* Infant 2011. **7**(3): p. 88-91.
177. NICE Clinical guidelines, *Epilepsies: diagnosis and management* 2012, NICE: www.nice.org.uk/guidance/cg137.
178. Shinnar, S. and J.M. Pellock, *Update on the epidemiology and prognosis of pediatric epilepsy.* J Child Neurol, 2002. **17 Suppl 1**: p. S4-17.
179. Udani, V., *Evaluation and management of intractable epilepsy.* Indian J Pediatr, 2000. **67**(1 Suppl): p. S61-70.
180. Murphy, J.V. and F. Dehkharghani, *Diagnosis of childhood seizure disorders.* Epilepsia, 1994. **35 Suppl 2**: p. S7-17.
181. Dunn, D.W., *Neuropsychiatric aspects of epilepsy in children.* Epilepsy Behav, 2003. **4**(2): p. 101-6.
182. Holmes, G.L., et al., *[Consequences of recurrent seizures during development].* Rev Neurol, 1997. **25**(141): p. 749-53.
183. Anderson, G.D., *Children versus adults: pharmacokinetic and adverse-effect differences.* Epilepsia, 2002. **43 Suppl 3**: p. 53-9.
184. Mattson, R.H., *The role of the old and the new antiepileptic drugs in special populations: mental and multiple handicaps.* Epilepsia, 1996. **37 Suppl 6**: p. S45-53.
185. Blume, W.T., *Uncontrolled epilepsy in children.* Epilepsy Res Suppl, 1992. **5**: p. 19-24.
186. Camfield, P.R. and C.S. Camfield, *Antiepileptic drug therapy: when is epilepsy truly intractable?* Epilepsia, 1996. **37 Suppl 1**: p. S60-5.
187. Holmes, G.L., *Seizure disorders in children.* Curr Opin Pediatr, 1993. **5**(6): p. 653-9.
188. Iinuma, K., *[General principles of treatment and effects of childhood intractable epilepsy].* Rinsho Shinkeigaku, 1999. **39**(1): p. 75-6.

189. Steinborn, B., *[Intractable epilepsy of childhood and its treatment].* Neurol Neurochir Pol, 2000. **33 Suppl 1**: p. 37-48.
190. Grimshaw, D., et al., *Subcutaneous midazolam, diamorphine and hyoscine infusion in palliative care of a child with neurodegenerative disease.* Child Care Health Dev, 1995. **21**(6): p. 377-81.
191. Scott, R.C., F.M. Besag, and B.G. Neville, *Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial.* Lancet, 1999. **353**(9153): p. 623-6.
192. NICE Clinical Guideline, *Spasticity in under 19s: management* 2012, NICE: www.nice.org.uk/guidance/cg145.
193. Gormley, M.E., Jr., L.E. Krach, and L. Piccini, *Spasticity management in the child with spastic quadriplegia.* Eur J Neurol, 2001. **8 Suppl 5**: p. 127-35.
194. Kojovic, M., C. Cordivari, and K. Bhatia, *Myoclonic disorders: a practical approach for diagnosis and treatment.* Ther Adv Neurol Disord, 2011. **4**(1): p. 47-62.
195. Baizabal-Carvallo, J.F. and F. Cardoso, *Chorea in children: etiology, diagnostic approach and management.* J Neural Transm (Vienna), 2020. **127**(10): p. 1323-1342.
196. Schlaggar, B.L. and J.W. Mink, *Movement disorders in children.* Pediatr Rev, 2003. **24**(2): p. 39-51.
197. Twycross, R., *Palliative Care Formulary*, A.W. R. Twycross, S. Charlesworth, and A. Dickman, Editor. 2002, Radcliffe Medical Press: Oxon. p. 339.
198. Gibson, F. and S. Hopkins, *Feeling sick is horrible, and being sick is very frightening...say Jasper and Polly (Pearman, 1998).* Eur J Oncol Nurs, 2005. **9**(1): p. 6-7.
199. Singh, P., S.S. Yoon, and B. Kuo, *Nausea: a review of pathophysiology and therapeutics.* Therap Adv Gastroenterol, 2016. **9**(1): p. 98-112.
200. Miller, M.K., M., *Management of the gastrointestinal tract in paediatric palliative medicine*, in *Oxford text book of palliative care for children* H.R. Goldman A, Lien S(eds), Editor. 2012, Oxford University Press: Oxford p. 271-283.
201. Markowitz, A.J. and M.W. Rabow, *Management of intractable nausea and vomiting in patients at the end of life: "I was feeling nauseous all of the time . . . nothing was working".* Jama, 2008. **299**(15): p. 1826.
202. Patel, B., et al., *Long-Term Daily Administration of Aprepitant for the Management of Intractable Nausea and Vomiting in Children With Life-Limiting Conditions: A Case Series.* J Pain Symptom Manage, 2021. **62**(3): p. e225-e231.
203. Smith, H.S., J.M. Smith, and A.R. Smith, *An overview of nausea/vomiting in palliative medicine.* Ann Palliat Med, 2012. **1**(2): p. 103-14.
204. *Domperidone: an alternative to metoclopramide.* Drug Ther Bull, 1988. **26**(15): p. 59-60.
205. *5HT3-receptor antagonists as antiemetics in cancer.* Drug Ther Bull, 2005. **43**(8): p. 57-62.
206. Cinquetti, M., P. Bonetti, and P. Bertamini, *[Current role of antidopaminergic drugs in pediatrics].* Pediatr Med Chir, 2000. **22**(1): p. 1-7.
207. Culy, C.R., N. Bhana, and G.L. Plosker, *Ondansetron: a review of its use as an antiemetic in children.* Paediatr Drugs, 2001. **3**(6): p. 441-79.
208. Roila, F., M. Aapro, and A. Stewart, *Optimal selection of antiemetics in children receiving cancer chemotherapy.* Support Care Cancer, 1998. **6**(3): p. 215-20.
209. Skinner, J. and A. Skinner, *Levomepromazine for nausea and vomiting in advanced cancer.* Hosp Med, 1999. **60**(8): p. 568-70.
210. Goksan, S., et al., *fMRI reveals neural activity overlap between adult and infant pain.* Elife, 2015. **4**.

211. St-Laurent-Gagnon, T., A.C. Bernard-Bonnin, and E. Villeneuve, *Pain evaluation in preschool children and by their parents.* Acta Paediatr, 1999. **88**(4): p. 422-7.
212. Tsze, D.S., et al., *Validation of self-report pain scales in children.* Pediatrics, 2013. **132**(4): p. e971-9.
213. Sun, T., et al., *A smartphone version of the Faces Pain Scale-Revised and the Color Analog Scale for postoperative pain assessment in children.* Paediatr Anaesth, 2015. **25**(12): p. 1264-73.
214. Tomlinson, D., et al., *A systematic review of faces scales for the self-report of pain intensity in children.* Pediatrics, 2010. **126**(5): p. e1168-98.
215. Wong and Baker. 2021 [cited 2021 9th December]; Available from: https://wongbakerfaces.org/wp-content/uploads/2015/06/FACES_English_Blue1.jpg.
216. Garra, G., et al., *Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients.* Acad Emerg Med, 2010. **17**(1): p. 50-4.
217. Varni, J.W., K.L. Thompson, and V. Hanson, *The Varni/Thompson Pediatric Pain Questionnaire. I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis.* Pain, 1987. **28**(1): p. 27-38.
218. Gauvain-Piquard, A., et al., *The development of the DEGR(R): A scale to assess pain in young children with cancer.* Eur J Pain, 1999. **3**(2): p. 165-176.
219. Hain R. Jenney M. Carter B. Davies R., *Measuring the Pain of Mucositis using Oucher and DEGR. .* J Palliat Care Med, 2015. **5**(4): p. 222.
220. Piaget, J., *The child's conception of physical causality*, in *The essential Piaget*, H.E. Gruber and J.J. Vaneche, Editors. 1977, Routledge and Keegan Paul: London and Henley.
221. von Baeyer, C.L., et al., *Systematic Review of Self-Report Measures of Pain Intensity in 3- and 4-Year-Old Children: Bridging a Period of Rapid Cognitive Development.* J Pain, 2017. **18**(9): p. 1017-1026.
222. Bennett, M., *Assessing pain in children in the perioperative setting.* J Perioper Pract, 2019. **29**(1-2): p. 9-16.
223. Cascella, M., et al., *The challenge of pain assessment in children with cognitive disabilities: Features and clinical applicability of different observational tools.* J Paediatr Child Health, 2019. **55**(2): p. 129-135.
224. Hummel, P., P. Lawlor-Klean, and M.G. Weiss, *Validity and reliability of the N-PASS assessment tool with acute pain.* J Perinatol, 2010. **30**(7): p. 474-8.
225. Hechler, T., et al., *Parents' perspective on symptoms, quality of life, characteristics of death and end-of-life decisions for children dying from cancer.* Klinische Padiatrie, 2008. **220**(3): p. 166-174.
226. Schechter, N.L., C.B. Berde, and M. Yaster, *Pain in infants, children, and adolescents: An overview.* Pain in Infants, Children, and Adolescents, 1993: p. 3-9.
227. Berde, C. and P. McGrath, *Pain measurement and Beecher's challenge: 50 years later.* Anesthesiology, 2009. **111**(3): p. 473-4.
228. McGrath, P., *Pain Control*, in *Oxford Textbook of Palliative Medicine*, G.H. D Doyle, NI Cherny, K Calman, Editor. 1998, Oxford University Press: Oxford. p. 775-789.
229. McGrath, P.A., *Children - not simply "Little adults".* The Path of Pain 1975-2005, 2005: p. 433-446.
230. McGrath, P.A., *Commentary: Psychological interventions for controlling children's pain: Challenges for evidence-based medicine.* Journal of Pediatric Psychology, 1999. **24**(2): p. 172-174.
231. Kuttner, L., *A child in pain. How to help, what to do.* 1996: Hartley & Marks Publishing Inc.

232. Kuttner, L., *Pain: an integrative approach*, in *Oxford Textbook of Palliative Care for Children*, H.R. Goldman A, Liben S, Editor. 2012, Oxford University Press: Oxford. p. 261-270.
233. Palermo, T.M. and C.T. Chambers, *Parent and family factors in pediatric chronic pain and disability: An integrative approach.* Pain, 2005. **119**(1-3): p. 1-4.
234. Palermo, T.M., D. Harrison, and J.L. Koh, *Effect of disease-related pain on the health-related quality of life of children and adolescents with cystic fibrosis.* Clin J Pain, 2006. **22**(6): p. 532-7.
235. WHO, *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*. 2012.
236. Treede, R.D., et al., *Neuropathic pain: Redefinition and a grading system for clinical and research purposes.* Neurology, 2008. **70**(18): p. 1630-1635.
237. Walco, G.A., et al., *Neuropathic pain in children: Special considerations.* Mayo Clinic Proceedings, 2010. **85**(3 SUPPL.).
238. Hauer, J., *Identifying and managing sources of pain and distress in children with neurological impairment.* Pediatric Annals, 2010. **39**(4): p. 198-205.
239. Hain, R.a.D., H, *Neurological Symptoms*. Textbook of Interdisciplinary Pediatric Palliative Care, ed. J.W.a.P.S. Hinds. 2010, Cambridge: Elsevier.
240. Klick, J.C. and J. Hauer, *Pediatric palliative care.* Current Problems in Pediatric and Adolescent Health Care, 2010. **40**(6): p. 120-151.
241. Houlihan, C.M., et al., *Bodily pain and health-related quality of life in children with cerebral palsy.* Dev Med Child Neurol, 2004. **46**(5): p. 305-10.
242. Kinami, H., et al., *A Devised Option of Neonatal Palliation for Compromised Tetralogy of Fallot with Absent Pulmonary Valve Syndrome.* Ann Thorac Cardiovasc Surg, 2019. **25**(5): p. 274-277.
243. Last, B.F. and A.M. van Veldhuizen, *Information about diagnosis and prognosis related to anxiety and depression in children with cancer aged 8-16 years.* Eur J Cancer, 1996. **32A**(2): p. 290-4.
244. Ziesenitz, V.C., et al., *Efficacy and Safety of Ibuprofen in Infants Aged Between 3 and 6 Months.* Paediatr Drugs, 2017. **19**(4): p. 277-290.
245. Friedrichsdorf S .J, *Multimodal analgesia in paediatric palliative care.*, in *Oxford Textbook of Palliative Care for Children,*, Hain R. Goldman A. Rapoport A. Meiring M., Editor. 2021: Oxford. p. 165.
246. Finnerup, N.B., et al., *Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis.* Lancet Neurol, 2015. **14**(2): p. 162-73.
247. Benini, F., et al., *Refractory symptoms in paediatric palliative care: can ketamine help?* Drugs Context, 2021. **10**.
248. Dale, O., et al., *Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis.* Anesth Analg, 2012. **115**(4): p. 934-43.
249. Bell, R.F. and E.A. Kalso, *Ketamine for pain management.* Pain Rep, 2018. **3**(5): p. e674.
250. Bell, R., C. Eccleston, and E. Kalso, *Ketamine as an adjuvant to opioids for cancer pain.* Cochrane Database Syst Rev, 2003(1): p. CD003351.
251. Taylor, M., et al., *Ketamine PCA for treatment of end-of-life neuropathic pain in pediatrics.* Am J Hosp Palliat Care, 2015. **32**(8): p. 841-8.
252. Webster, L.R. and M.J. Walker, *Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain.* Am J Ther, 2006. **13**(4): p. 300-5.
253. Finnerup, N.B., R. Kuner, and T.S. Jensen, *Neuropathic Pain: From Mechanisms to Treatment.* Physiol Rev, 2021. **101**(1): p. 259-301.

254. Kaguelidou, F., et al., *Non-inferiority double-blind randomised controlled trial comparing gabapentin versus tramadol for the treatment of chronic neuropathic or mixed pain in children and adolescents: the GABA-1 trial-a study protocol.* BMJ Open, 2019. **9**(2): p. e023296.
255. Moulin, D., et al., *Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society.* Pain Res Manag, 2014. **19**(6): p. 328-35.
256. Molero, Y., et al., *Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: population based cohort study in Sweden.* BMJ, 2019. **365**: p. l2147.
257. Wong, S.S. and T.E. Wilens, *Medical Cannabinoids in Children and Adolescents: A Systematic Review.* Pediatrics, 2017. **140**(5).
258. O'Mahony SM. Dinan T. G. Cryan J. F., *The gut microbiota as a key regulator of visceral pain.* Pain, 2017. **158 Suppl 1**: p. S19-S28.
259. Tutelman, P.R., et al., *Pain in Children With Cancer: Prevalence, Characteristics, and Parent Management.* Clin J Pain, 2018. **34**(3): p. 198-206.
260. Axelrod, D.J. and B. Reville, *Using methadone to treat opioid-induced hyperalgesia and refractory pain.* J Opioid Manag, 2007. **3**(2): p. 113-4.
261. Velayudhan A. Bellingham G. and Morley-Forster P., *Opioid-induced hyperalgesia. .* Continuing Education in Anaesthesia, Critical Care & Pain, , 2014. **14**(3): p. 125-129.
262. Sasaki, M., et al., *Serotonin Plays a Key Role in the Development of Opioid-Induced Hyperalgesia in Mice.* J Pain, 2021. **22**(6): p. 715-729.
263. Colvin, L.A., F. Bull, and T.G. Hales, *Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia.* Lancet, 2019. **393**(10180): p. 1558-1568.
264. Mott, C., et al., *Methadone for Analgesia in Children with Life-Limiting Illness: Experience from a Tertiary Children's Health Service.* Children (Basel), 2018. **5**(7).
265. Snaman, J.M., et al., *Pediatric Oncology: Managing Pain at the End of Life.* Paediatr Drugs, 2016. **18**(3): p. 161-80.
266. Mherekumombe, M.F. and J.J. Collins, *Patient-controlled analgesia for children at home.* J Pain Symptom Manage, 2015. **49**(5): p. 923-7.
267. Collins, J.J., et al., *Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone.* J Pediatr, 1996. **129**(5): p. 722-8.
268. Grossoehme, D.H., et al., *A Retrospective Examination of Home PCA Use and Parental Satisfaction With Pediatric Palliative Care Patients.* Am J Hosp Palliat Care, 2021: p. 10499091211034421.
269. Fortier, M.A., et al., *Children's cancer pain in a world of the opioid epidemic: Challenges and opportunities.* Pediatr Blood Cancer, 2020. **67**(4): p. e28124.
270. Lozano J. and de Leon-Casasola O.A., *Indications for intrathecal therapy in cancer patients. .* Techniques in Regional Anesthesia and Pain Management, 2011. **15**(4): p. 147-14.
271. Brook P. Connell J. and Pickering T., *Oxford handbook of pain management.* 2011, Oxford: Oxford University Press.
272. De León-Casasola O., *Intrathecal therapy for cancer pain management.* Revista de la Sociedad Española del Dolor,, 2010. **17**(3): p. 162-168.
273. Sindt, J.E., et al., *Initial Intrathecal Dose Titration and Predictors of Early Dose Escalation in Patients With Cancer Using a 100:1 Oral to Intrathecal Morphine Conversion Ratio.* Neuromodulation, 2021. **24**(7): p. 1157-1166.

274. Raffaela Di Napoli. Gennaro Esposito. Marco Cascella. *Intrathecal Catheter*. StatPearls, 2021.
275. Amy Givler. Harshil Bhatt. Patricia A. Maani-Fogelman. *The Importance Of Cultural Competence in Pain and Palliative Care*. StatPearls, 2021.
276. Bhumik Patel. Julie Bayliss. Renee McCulloch. Finella Criag. Dilini Rajapakse. Michelle Koh. Margaret Comac. June Hemsley. Chloe Dewar. Charlotte Bell. Myra Bluebond-Langner., *Use of ambulatory PCA for children and young people with advanced cancer: evaluation of Use and Outcome*, Archives of Disease in Childhood, Editor 2021, BMJ Journal. p. 60.
277. Rajapakse, D., C. Liossi, and R.F. Howard, *Presentation and management of chronic pain.* Arch Dis Child, 2014. **99**(5): p. 474-80.
278. Gatchel, R.J., et al., *The biopsychosocial approach to chronic pain: scientific advances and future directions.* Psychol Bull, 2007. **133**(4): p. 581-624.
279. Pincus, T., et al., *Cognitive and affective reassurance and patient outcomes in primary care: a systematic review.* Pain, 2013. **154**(11): p. 2407-2416.
280. Zernikow, B., et al., *Pediatric palliative care: use of opioids for the management of pain.* Paediatr Drugs, 2009. **11**(2): p. 129-51.
281. Gregoire, M.C. and G.A. Finley, *Drugs for chronic pain in children: a commentary on clinical practice and the absence of evidence.* Pain Res Manag, 2013. **18**(1): p. 47-50.
282. Howard, R.F., S. Wiener, and S.M. Walker, *Neuropathic pain in children.* Arch Dis Child, 2014. **99**(1): p. 84-9.
283. Moore, R.A., et al., *Amitriptyline for neuropathic pain and fibromyalgia in adults.* Cochrane Database Syst Rev, 2012. **12**: p. CD008242.
284. Vondracek, P., et al., *Efficacy of pregabalin in neuropathic pain in paediatric oncological patients.* Eur J Paediatr Neurol, 2009. **13**(4): p. 332-6.
285. Fisher, E., et al., *Psychological therapies for the management of chronic and recurrent pain in children and adolescents.* Cochrane Database Syst Rev, 2018. **9**: p. CD003968.
286. Jamieson-Lega, K., R. Berry, and C.A. Brown, *Pacing: a concept analysis of the chronic pain intervention.* Pain Res Manag, 2013. **18**(4): p. 207-13.
287. Malanga, G.A., N. Yan, and J. Stark, *Mechanisms and efficacy of heat and cold therapies for musculoskeletal injury.* Postgrad Med, 2015. **127**(1): p. 57-65.
288. McCabe, C., *Mirror visual feedback therapy. A practical approach.* J Hand Ther, 2011. **24**(2): p. 170-8; quiz 179.
289. Children's Hospital of Philadelphia. *Amplified Musculoskeletal Pain Syndrome Desensitization Techniques*. https://www.chop.edu/video/amplified-musculoskeletal-pain-syndrome-desensitization-techniques 2022.
290. Saunders C. & Baines M. , *Living With Dying: The Management Of Terminal Disease*. 1983, Oxford: Oxford University Press.
291. Chi-Keong Ong & Forbes *Embracing Cicely Saunders's concept of total pain*, BMJ, Editor 2005, BMJ: https://www.bmj.com/content/331/7516/576.5. p. Vol 10; 331(7516) pages 576 – 577.
292. Cole A., *Children's pain: we can make it better?*, in *Frontline*2018: https://www.csp.org.uk/frontline/article/childrens-pain-we-can-make-it-better.
293. Emslie, G.J., et al., *Fluoxetine Versus Placebo in Preventing Relapse of Major Depression in Children and Adolescents.* Am J Psychiatry, 2008.
294. Birmaher, B., et al., *Fluoxetine for the treatment of childhood anxiety disorders.* J Am Acad Child Adolesc Psychiatry, 2003. **42**(4): p. 415-23.
295. Jick, H., J.A. Kaye, and S.S. Jick, *Antidepressants and the risk of suicidal behaviors.* JAMA, 2004. **292**(3): p. 338-43.

296. Kersun, L.S. and E. Shemesh, *Depression and anxiety in children at the end of life.* Pediatr Clin North Am, 2007. **54**(5): p. 691-708, xi.
297. Dietz, I., et al., *Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review.* BMC Palliat Care, 2013. **12**: p. 2.
298. Usala, T., et al., *Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis.* Eur Neuropsychopharmacol, 2008. **18**(1): p. 62-73.
299. NICE, *Depression in children: Scenario: Moderate to severe depression.* , 2020: https://cks.nice.org.uk/topics/depression-in-children/management/moderate-to-severe-depression/
300. NICE, *End of life care in children: Scenario: Managing specific care issues.* , 2020: https://cks.nice.org.uk/topics/end-of-life-care-in-children/management/managing-specific-care-issues/
301. Muriel, A., McCulloch, R. and Hammel, J, , *Depression, anxiety and delirium.* , in *Oxford Textbook of Palliative Care for children* A.H. Goldman, R. Liben, S. eds. , Editor. 2012, Oxford University Press: Oxford. p. 218-233.
302. Leonte, K.e.a. *Pharmacotherapy for anxiety disorders in children and adolescents*. UPTODATE, 2021. https://www-uptodate-com.abc.cardiff.ac.uk/contents/pharmacotherapy-for-anxiety-disorders-in-children-and-adolescents?search=child%20anxiety&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
303. Twycross, R.a.W., A. , *Symptom Management: Psychological & Neurological*, in *Introducing Palliative Care* Palliativedrugs.com., Editor. p. 185-210.
304. Medic, G., M. Wille, and M.E. Hemels, *Short- and long-term health consequences of sleep disruption.* Nat Sci Sleep, 2017. **9**: p. 151-161.
305. American Academy of Sleep Medicine, *International Classification of Sleep Disorders; American Academy of Sleep Medicine*, 2014: Darien, IL, USA.
306. Mol, E.M., et al., *The use of night orthoses in cerebral palsy treatment: sleep disturbance in children and parental burden or not?* Res Dev Disabil, 2012. **33**(2): p. 341-9.
307. Romeo, D.M., et al., *Sleep disorders in children with cerebral palsy: neurodevelopmental and behavioral correlates.* Sleep Med, 2014. **15**(2): p. 213-8.
308. Tietze, A.L., et al., *Sleep disturbances in children with multiple disabilities.* Sleep Med Rev, 2012. **16**(2): p. 117-27.
309. Kohrman, M.H. and P.R. Carney, *Sleep-related disorders in neurologic disease during childhood.* Pediatr Neurol, 2000. **23**(2): p. 107-13.
310. Tolaymat, A. and Z. Liu, *Sleep Disorders in Childhood Neurological Diseases.* Children (Basel), 2017. **4**(10).
311. Dorris, L., et al., *Sleep problems in children with neurological disorders.* Dev Neurorehabil, 2008. **11**(2): p. 95-114.
312. Dreier, L.A., et al., *Insights into the Frequency and Distinguishing Features of Sleep Disorders in Pediatric Palliative Care Incorporating a Systematic Sleep Protocol.* Children (Basel), 2021. **8**(1).
313. Hauer J.M. , *Caring for Children Who Have Severe Neurological Impairment. A Life With Grace*. p. Pages 296-301.
314. Long, A.C., V. Krishnamurthy, and T.M. Palermo, *Sleep disturbances in school-age children with chronic pain.* J Pediatr Psychol, 2008. **33**(3): p. 258-68.

315. Hugel, H., et al., *The prevalence, key causes and management of insomnia in palliative care patients.* J Pain Symptom Manage, 2004. **27**(4): p. 316-21.
316. Wilson, S.J., et al., *British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders.* J Psychopharmacol, 2010. **24**(11): p. 1577-601.
317. Kvale, E.A. and J.L. Shuster, *Sleep disturbance in supportive care of cancer: a review.* J Palliat Med, 2006. **9**(2): p. 437-50.
318. Sateia, M.J. and B.J. Lang, *Sleep and cancer: recent developments.* Curr Oncol Rep, 2008. **10**(4): p. 309-18.
319. Delgado-Guay, M., et al., *Association between self-reported sleep disturbance and other symptoms in patients with advanced cancer.* J Pain Symptom Manage, 2011. **41**(5): p. 819-27.
320. Wells-Di Gregorio S., G.J., Marks D., Taylor R., Coller K. & Magalang U.,, *Worry as a Significant Predictor of Insomnia among Palliative Care Patients with Advanced Cancer.* J Pain Symptom Manage, 2010. **23**(1): p. 46-53.
321. Mystakidou, K., et al., *How is sleep quality affected by the psychological and symptom distress of advanced cancer patients?* Palliat Med, 2009. **23**(1): p. 46-53.
322. Eyigor, S., C. Eyigor, and R. Uslu, *Assessment of pain, fatigue, sleep and quality of life (QoL) in elderly hospitalized cancer patients.* Arch Gerontol Geriatr, 2010. **51**(3): p. e57-61.
323. Morin C.M., S.J., Ouellet M. & Daley M. ,, *Insomnia*, in *Handbook of Psychology*. 2003, John Wiley & Sons, Inc.
324. Morin, C.M. and R. Benca, *Chronic insomnia.* Lancet, 2012. **379**(9821): p. 1129-41.
325. Hain R and Jassal S, *Oxford handbook of paediatric palliative medicine.* 2nd ed. 2010: Oxford University Press
326. Moturi, S. and K. Avis, *Assessment and treatment of common pediatric sleep disorders.* Psychiatry (Edgmont), 2010. **7**(6): p. 24-37.
327. Bruni, O., et al., *The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence.* J Sleep Res, 1996. **5**(4): p. 251-61.
328. McDonald, A. and D. Joseph, *Paediatric neurodisability and sleep disorders: clinical pathways and management strategies.* BMJ Paediatr Open, 2019. **3**(1): p. e000290.
329. Merz, E.L. and L. Tomfohr-Madsen, *Sleep Disruption in Pediatric Cancer Survivors: Conceptual Framework and Opportunities for Clinical Assessment and Behavioral Treatment.* Am J Lifestyle Med, 2018. **12**(4): p. 311-323.
330. Sagha Zadeh, R., et al., *Non-pharmacological solutions to sleep and circadian rhythm disruption: voiced bedside experiences of hospice and end-of-life staff caregivers.* BMC Palliat Care, 2018. **17**(1): p. 131.
331. Jan, J.E. and R.D. Freeman, *Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: what have we learned in the last decade?* Dev Med Child Neurol, 2004. **46**(11): p. 776-82.
332. Hoebert, M., et al., *Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia.* J Pineal Res, 2009. **47**(1): p. 1-7.
333. Pallija, G., M. Mondozzi, and A.A. Webb, *Skin care of the pediatric patient.* J Pediatr Nurs, 1999. **14**(2): p. 80-7.
334. Quigley, S.M. and M.A. Curley, *Skin integrity in the pediatric population: preventing and managing pressure ulcers.* J Soc Pediatr Nurs, 1996. **1**(1): p. 7-18.

335. Willock, J., et al., *Identifying the characteristics of children with pressure ulcers.* Nurs Times, 2005. **101**(11): p. 40-3.
336. Andrew Wilcock and Robert Twycross, *Symptom management in advanced cancer*. Third ed. 2001: Radcliffe medical Press.
337. BNF, *British National Formulary*. 77 ed, ed. R. BMA. 2019, London: BMJ Publishing Group, RPS Publishing,.
338. BNF, *British National Formulary for Children*, ed. R. BMA, RCPCH, NPPG. 2018-19, London: BMJ Publishing Group, RPS Publishing, and RCPCH Publications.
339. NNF7, *Neonatal Formulary 7*. BMJ Books. 2015: Blackwell Wiley Publishing.
340. Twycross R, Wilcock A, and Howard P, *Palliative Care Formulary (PCF 6).* 6th ed. 2017: Nottingham: Palliativedrugs.com Ltd.
341. RCPCH, N., *'Medicines for Children'*. 2nd ed. ed. 2003: RCPCH Publications limited.
342. Markey, K.A., et al., *Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions.* Lancet Neurol, 2016. **15**(1): p. 78-91.
343. Shinnar, S., et al., *Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts.* J Pediatr, 1985. **107**(1): p. 31-7.
344. Asiedu, M.N., et al., *Inhibition of carbonic anhydrase augments GABAA receptor-mediated analgesia via a spinal mechanism of action.* J Pain, 2014. **15**(4): p. 395-406.
345. Rebecca White and Vicky Bradnam, *Handbook of Drug administration via Enteral Feeding Tubes*. 3rd ed, ed. B.P.N. Group. 2015: Pharmaceutical Press.
346. Dickman, A. and J. Schneider, *The Syringe Driver. Continuous Infusions in Palliative Care*. 4th ed. 2016: Oxford University Press.
347. Von Heijne, M., et al., *Propofol or propofol--alfentanil anesthesia for painful procedures in the pediatric oncology ward.* Paediatr Anaesth, 2004. **14**(8): p. 670-5.
348. Duncan, A., *The use of fentanyl and alfentanil sprays for episodic pain.* Palliat Med, 2002. **16**(6): p. 550.
349. Selby & York Palliative Care Team & Pharmacy Group. *Prescribing and administration information for Alfentanil spray* 2007; Available from: www.yacpalliativecare.co.uk/documents/download21.pdf
350. Urch, C., Carr S, Minton O, *Retrospective review of use of alfentanil in hospital palliative care settings. .* Palliative Medicine, (2004. **18**: p. 516-19.
351. Hershey, A.D., et al., *Effectiveness of amitriptyline in the prophylactic management of childhood headaches.* Headache, 2000. **40**(7): p. 539-49.
352. Heiligenstein, E. and B.L. Steif, *Tricyclics for pain.* J Am Acad Child Adolesc Psychiatry, 1989. **28**(5): p. 804-5.
353. Kaminski, A., et al., *Antidepressants for the treatment of abdominal pain-related functional gastrointestinal disorders in children and adolescents.* Cochrane Database Syst Rev, 2011(7): p. CD008013.
354. Korterink, J., et al., *Childhood functional abdominal pain: mechanisms and management.* Nat Rev Gastroenterol Hepatol, 2015. **12**(3): p. 159-71.
355. Gibson, P. and A. Vertigan, *Management of chronic refractory cough.* British Medical Journal 2015. **351**(h5590).
356. Gore, L., et al., *Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability.* Pediatr Blood Cancer, 2009. **52**(2): p. 242-7.
357. Murphy D et al, *Aprepitant is efficacious and safe in young teenagers. .* Pediatr Blood Cancer, 2011. **57**(5): p. 734-735 (Abs).

358. Williams D et al, *Extended use of aprepitant in pediatric patients.* Biology of Blood and Marrow Transplantation, 2012. **18**(2): p. Suppl 2 S378 (Abs).
359. Choi, M.R., C. Jiles, and N.L. Seibel, *Aprepitant use in children, adolescents, and young adults for the control of chemotherapy-induced nausea and vomiting (CINV).* J Pediatr Hematol Oncol, 2010. **32**(7): p. e268-71.
360. Murphy C et al, *NK1 receptor antagonism ameliorates nausea and emesis in typical and atypical variants of treatment refractory cyclical vomiting syndrome.* J Pediatr Gastroenterology Nutr,, 2006. **42**(5): p. e13-14.
361. Kang, H.J., et al., *Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial.* Lancet Oncol, 2015. **16**(4): p. 385-94.
362. Heisler, M., et al., *Randomized double-blind trial of sublingual atropine vs. placebo for the management of death rattle.* J Pain Symptom Manage, 2013. **45**(1): p. 14-22.
363. Kintzel, P.E., et al., *Anticholinergic medications for managing noisy respirations in adult hospice patients.* Am J Health Syst Pharm, 2009. **66**(5): p. 458-64.
364. Norderyd, J., et al., *Sublingual administration of atropine eyedrops in children with excessive drooling - a pilot study.* Int J Paediatr Dent, 2015.
365. Wee, B. and R. Hillier, *Interventions for noisy breathing in patients near to death.* Cochrane Database Syst Rev, 2008(1): p. CD005177.
366. Dias, B.L.S., A.R. Fernandes, and H.S.F. Maia, *Treatment of drooling with sublingual atropine sulfate in children and adolescents with cerebral palsy.* Arq Neuropsiquiatr, 2017. **75**(5): p. 282-287.
367. Norderyd, J., et al., *Sublingual administration of atropine eyedrops in children with excessive drooling - a pilot study.* Int J Paediatr Dent, 2017. **27**(1): p. 22-29.
368. Azapagasi, *Sublinguinal atropine*, in *Pediatric Pulmonology*2017. p. 52.
369. Rapoport, A., *Sublingual atropine drops for the treatment of pediatric sialorrhea.* J Pain Symptom Manage, 2010. **40**(5): p. 783-8.
370. Dachy, B. and B. Dan, *Electrophysiological assessment of the effect of intrathecal baclofen in dystonic children.* Clin Neurophysiol, 2004. **115**(4): p. 774-8.
371. Campistol, J., *[Orally administered drugs in the treatment of spasticity].* Rev Neurol, 2003. **37**(1): p. 70-4.
372. Delgado, M.R., et al., *Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.* Neurology. **74**(4): p. 336-43.
373. Hansel, D.E., et al., *Oral baclofen in cerebral palsy: possible seizure potentiation?* Pediatric Neurology, 2003. **29**(3 SU -): p. 203-206.
374. Jones, R.F. and J.W. Lance, *Bacloffen (Lioresal) in the long-term management of spasticity.* Med J Aust, 1976. **1**(18): p. 654-7.
375. Pascual-Pascual, S.I., *[The study and treatment of dystonias in childhood].* Rev Neurol, 2006. **43 Suppl 1**: p. S161-8.
376. Patel, D.R. and O. Soyode, *Pharmacologic interventions for reducing spasticity in cerebral palsy.* Indian J Pediatr, 2005. **72**(10): p. 869-72.
377. Coffey, R.e.a., *Abrupt withdrawal from intrathecal baclofen: recognition and management of a potentially life threatening syndrome. .* Archives of Physical Medicine and Rehabilitation, 2002. **83**: p. 735-41.

378. Remi, C. and E. Alrecht, *Subcutaneous use of baclofen. .* Journal of Pain and Symptom Management 2014. **48**(e1-3).
379. Kamm Michael, A.e.a., *Oral Bisacodyl is Effective and Well-Tolerated in Patients With Chronic Constipation.* Clincal Gastroenterology and Hepatology, 2011. **9**(01): p. 557-583.
380. Dahan, A., L. Aarts, and T.W. Smith, *Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression.* Anesthesiology, 2010. **112**(1): p. 226-38.
381. Ruggiero, A., et al., *Efficacy and safety of transdermal buprenorphine in the management of children with cancer-related pain.* Pediatr Blood Cancer, 2013. **60**(3): p. 433-7.
382. Michel, E., B.J. Anderson, and B. Zernikow, *Buprenorphine TTS for children--a review of the drug's clinical pharmacology.* Paediatr Anaesth, 2011. **21**(3): p. 280-90.
383. Davis, M.P., *Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain.* J Support Oncol, 2012. **10**(6): p. 209-19.
384. Kress, H.G., *Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine.* Eur J Pain, 2009. **13**(3): p. 219-30.
385. Cooper, T.E., et al., *Opioids for chronic non-cancer pain in children and adolescents.* Cochrane Database Syst Rev, 2017. **7**: p. CD012538.
386. Wiffen, P.J., et al., *Opioids for cancer-related pain in children and adolescents.* Cochrane Database Syst Rev, 2017. **7**: p. CD012564.
387. Chang, K.Y., et al., *Comparison of intravenous patient-controlled analgesia with buprenorphine versus morphine after lumbar spinal fusion--a prospective randomized clinical trial.* Acta Anaesthesiol Taiwan, 2006. **44**(3): p. 153-9.
388. Zanette, G., et al., *Respiratory depression following administration of low dose buprenorphine as postoperative analgesic after fentanyl balanced anaesthesia.* Paediatr Anaesth, 1996. **6**(5): p. 419-22.
389. Maunuksela, E.L., R. Korpela, and K.T. Olkkola, *Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain of children.* Br J Anaesth, 1988. **60**(1): p. 48-55.
390. Olkkola, K.T., M.A. Leijala, and E.L. Maunuksela, *Paediatric ventilatory effects of morphine and buprenorphine revisited.* Paediatr Anaesth, 1995. **5**(5): p. 303-5.
391. Hamunen, K., K.T. Olkkola, and E.L. Maunuksela, *Comparison of the ventilatory effects of morphine and buprenorphine in children.* Acta Anaesthesiol Scand, 1993. **37**(5): p. 449-53.
392. van Dorp, E., et al., *Naloxone reversal of buprenorphine-induced respiratory depression.* Anesthesiology, 2006. **105**(1): p. 51-7.
393. Yassen, A., et al., *Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone : a study in healthy volunteers.* Clin Pharmacokinet, 2007. **46**(11): p. 965-80.
394. Colvin, L. and M. Fallon, *Challenges in cancer pain management--bone pain.* Eur J Cancer, 2008. **44**(8): p. 1083-90.
395. Kienast, H.W. and L.D. Boshes, *Clinical trials of carbamazepine in suppressing pain.* Headache, 1968. **8**(1): p. 1-5.
396. Klepstad, P., et al., *Pain and pain treatments in European palliative care units. A cross sectional survey from the European Association for Palliative Care Research Network.* Palliat Med, 2005. **19**(6): p. 477-84.
397. Swerdlow, M., *The treatment of "shooting" pain.* Postgrad Med J, 1980. **56**(653): p. 159-61.
398. Ren, Z., et al., *Carbamazepine Withdrawal-induced Hyperalgesia in Chronic Neuropathic Pain.* Pain Physician, 2015. **18**(6): p. E1127-30.

399. Due, M.R., et al., *Carbamazepine potentiates the effectiveness of morphine in a rodent model of neuropathic pain.* PLoS One, 2014. **9**(9): p. e107399.
400. Lynch, P.M., et al., *The safety and efficacy of celecoxib in children with familial adenomatous polyposis.* Am J Gastroenterol. **105**(6): p. 1437-43.
401. Foeldvari, I., et al., *A prospective study comparing celecoxib with naproxen in children with juvenile rheumatoid arthritis.* J Rheumatol, 2009. **36**(1): p. 174-82.
402. Stempak, D., et al., *Single-dose and steady-state pharmacokinetics of celecoxib in children.* Clin Pharmacol Ther, 2002. **72**(5): p. 490-7.
403. Drugs.com, *http://www.drugs.com/dosage/celecoxib.html*, 2014.
404. Song, G.G., et al., *Relative efficacy and tolerability of etoricoxib, celecoxib, and naproxen in the treatment of osteoarthritis : A Bayesian network meta-analysis of randomized controlled trials based on patient withdrawal.* Z Rheumatol, 2016. **75**(5): p. 508-516.
405. Rattray, B., D.J. Nugent, and G. Young, *Celecoxib in the treatment of haemophilic synovitis, target joints, and pain in adults and children with haemophilia.* Haemophilia, 2006. **12**(5): p. 514-7.
406. Krishnaswami, S., et al., *Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis.* J Clin Pharmacol, 2012. **52**(8): p. 1134-49.
407. Murto, K., et al., *Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study.* Can J Anaesth, 2015. **62**(7): p. 785-97.
408. Jones, D.P. and E.A. Jones, *Drugs for Insomnia.* Can Med Assoc J, 1963. **89**: p. 1331.
409. Pandolfini, C. and M. Bonati, *A literature review on off-label drug use in children.* Eur J Pediatr, 2005. **164**(9): p. 552-8.
410. Weiss, S., *Sedation of pediatric patients for nuclear medicine procedures.* Semin Nucl Med, 1993. **23**(3): p. 190-8.
411. Hindley, D., et al., *Audit of the use of chloral hydrate as an acute treatment for childhood seizures'.* Dev Med Child Neurol, 2005. **47**(3): p. 212-3.
412. Krsek, P., et al., *Successful treatment of Ohtahara syndrome with chloral hydrate.* Pediatr Neurol, 2002. **27**(5): p. 388-91.
413. Lampl, Y., et al., *Chloral hydrate in intractable status epilepticus.* Ann Emerg Med, 1990. **19**(6): p. 674-6.
414. Vaillancourt, R., et al., *Successful treatment of a seizure disorder with chronic high-dose chloral hydrate: a pediatric case report.* J Palliat Care, 2010. **26**(4): p. 311-3.
415. Allen, N.M., et al., *Status dystonicus: a practice guide.* Dev Med Child Neurol, 2014. **56**(2): p. 105-12.
416. Powell, T.G. and L. Rosenbloom, *The use of chloral hydrate for refractory childhood epilepsy.* Dev Med Child Neurol, 1983. **25**(4): p. 524-6.
417. Pranzatelli, M.R. and E.D. Tate, *Chloral hydrate for progressive myoclonus epilepsy: a new look at an old drug.* Pediatr Neurol, 2001. **25**(5): p. 385-9.
418. Joffe, A.R., et al., *Chloral hydrate enteral infusion for sedation in ventilated children: the CHOSEN pilot study.* Crit Care, 2017. **21**(1): p. 290.
419. Friedman, N.L., *Hiccups: a treatment review.* Pharmacotherapy, 1996. **16**(6): p. 986-95.
420. Jassal, S., ed. *Basic Symptom Control in Paediatric Palliative Care*. 9th ed. Rainbow's Hospice Symptom Control Manual, ed. S. Jassal. 2013.
421. Graham-Pole, J., et al., *Antiemetics in children receiving cancer chemotherapy: a double-blind prospective randomized study comparing metoclopramide with chlorpromazine.* J Clin Oncol, 1986. **4**(7): p. 1110-3.
422. Launois, S., et al., *Hiccup in adults: an overview.* Eur Respir J, 1993. **6**(4): p. 563-75.

423. Lewis, J.H., *Hiccups: causes and cures.* J Clin Gastroenterol, 1985. **7**(6): p. 539-52.
424. Lipsky, M.S., *Chronic hiccups.* Am Fam Physician, 1986. **34**(5): p. 173-7.
425. Williamson, B.W. and I.M. MacIntyre, *Management of intractable hiccup.* Br Med J, 1977. **2**(6085): p. 501-3.
426. Bascom, P.B., J.L. Bordley, and A.J. Lawton, *High-dose neuroleptics and neuroleptic rotation for agitated delirium near the end of life.* Am J Hosp Palliat Care, 2014. **31**(8): p. 808-11.
427. Chatha, R., et al., *Using the "benzodiazepine switch" in difficult childhood epilepsy.* Dev Med Child Neurol, 2008. **50**(8): p. 635-6.
428. Burns, M.L., et al., *Therapeutic Drug Monitoring of Clobazam and Its Metabolite-Impact of Age and Comedication on Pharmacokinetic Variability.* Ther Drug Monit, 2016. **38**(3): p. 350-7.
429. Lwin, E.M., et al., *Stability Studies of Extemporaneously Compounded Clobazam Oral Suspension.* Ann Pharmacother, 2016. **50**(2): p. 155-6.
430. MartindaleOnline, *The Complete Drug Reference*, S.C. Sweetman, Editor, Pharmaceutical Press.
431. Ashton, H., *Guidelines for the rational use of benzodiazepines. When and what to use.* Drugs, 1994. **48**(1): p. 25-40.
432. Schneider, J.J., P. Good, and P.J. Ravenscroft, *Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion.* J Pain Symptom Manage, 2006. **31**(6): p. 563-7.
433. Hugel, H., J.E. Ellershaw, and A. Dickman, *Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain.* J Pain Symptom Manage, 2003. **26**(6): p. 1073-4.
434. Cui, Y., et al., *Efficacy evaluation of clonazepam for symptom remission in burning mouth syndrome: a meta-analysis.* Oral Dis, 2016. **22**(6): p. 503-11.
435. Kuten-Shorrer, M., et al., *Safety and tolerability of topical clonazepam solution for management of oral dysesthesia.* Oral Surg Oral Med Oral Pathol Oral Radiol, 2017. **124**(2): p. 146-151.
436. Bowman, V., *Guidelines for the use of Clonidine patches at BCH*, B.C. Hospital, Editor 2015, BCH.
437. Larsson, P., et al., *Oral bioavailability of clonidine in children.* Paediatr Anaesth, 2011. **21**(3): p. 335-40.
438. Lambert, P., et al., *Clonidine premedication for postoperative analgesia in children.* Cochrane Database Syst Rev, 2014. **1**: p. CD009633.
439. Dahmani, S., et al., *Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies.* Acta Anaesthesiol Scand, 2010. **54**(4): p. 397-402.
440. Bergendahl, H., P.A. Lonnqvist, and S. Eksborg, *Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication.* Acta Anaesthesiol Scand, 2006. **50**(2): p. 135-43.
441. Mitra, S., S. Kazal, and L.K. Anand, *Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial.* Indian Pediatr, 2014. **51**(2): p. 113-8.
442. Mukherjee, A., *Characterization of alpha 2-adrenergic receptors in human platelets by binding of a radioactive ligand [3H]yohimbine.* Biochim Biophys Acta, 1981. **676**(2): p. 148-54.
443. Freeman, K.O., et al., *Analgesia for paediatric tonsillectomy and adenoidectomy with intramuscular clonidine.* Paediatr Anaesth, 2002. **12**(7): p. 617-20.
444. Arenas-Lopez, S., et al., *Use of oral clonidine for sedation in ventilated paediatric intensive care patients.* Intensive Care Med, 2004. **30**(8): p. 1625-9.

445. Ambrose, C., et al., *Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability.* Br J Anaesth, 2000. **84**(6): p. 794-6.
446. Honey, B.L., et al., *Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients.* Ann Pharmacother, 2009. **43**(9): p. 1506-11.
447. Schnabel, A., et al., *Efficacy and safety of clonidine as additive for caudal regional anesthesia: a quantitative systematic review of randomized controlled trials.* Paediatr Anaesth, 2011. **21**(12): p. 1219-30.
448. Lubsch, L., et al., *Oral baclofen and clonidine for treatment of spasticity in children.* J Child Neurol, 2006. **21**(12): p. 1090-2.
449. Nguyen, M., et al., *A review of the use of clonidine as a sleep aid in the child and adolescent population.* Clin Pediatr (Phila), 2014. **53**(3): p. 211-6.
450. Potts, A.L., et al., *Clonidine disposition in children; a population analysis.* Paediatr Anaesth, 2007. **17**(10): p. 924-33.
451. Sassarini, J. and M.A. Lumsden, *Non-hormonal management of vasomotor symptoms.* Climacteric, 2013. **16 Suppl 1**: p. 31-6.
452. Hunseler, C., et al., *Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial.* Pediatr Crit Care Med, 2014. **15**(6): p. 511-22.
453. Sanger, T.D., et al., *Definition and classification of hyperkinetic movements in childhood.* Mov Disord, 2010. **25**(11): p. 1538-49.
454. Basker, S., G. Singh, and R. Jacob, *Clonidine in paediatrics - a review.* Indian J Anaesth, 2009. **53**(3): p. 270-80.
455. Bartz, L., et al., *Subcutaneous administration of drugs in palliative care: results of a systematic observational study.* J Pain Symptom Manage, 2014. **48**(4): p. 540-7.
456. Goldenberg, G., T. Bharathan, and I. Shifrin, *Transdermal clonidine in patients with swallowing dysfunction.* J Palliat Med, 2014. **17**(9): p. 1042-4.
457. McCluggage, H.L., *Changing from continuous SC to transdermal clonidine to treat dystonia in a teenage boy with end-stage leucodystrophy.* BMJ Support Palliat Care, 2018. **8**(4): p. 433-435.
458. Ragnarsson, C. and E. Norman, *Implementation of Clonidine as a anew sedative and analgesic drug in the NICU-A Retrospective report on medical records.* Archives Diseases of Childhood, 2015. **101(1)**.
459. Neubert, A. and M.A. Baarslag, *The CLOSED trial; Clonidine compared with midazolam for SEDation of paediatric patients in the intensive care unit: study protocol for a multicentre randomised controlled trial. .* BMJ Open Sport Exerc Med, 2017. **7(6)**.
460. Harland, C.C. and P.S. Mortimer, *Laxative-induced contact dermatitis.* Contact Dermatitis, 1992. **27**(4): p. 268-9.
461. Smith, H.S., *Opioid metabolism.* Mayo Clin Proc, 2009. **84**(7): p. 613-24.
462. Williams, D.G., A. Patel, and R.F. Howard, *Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability.* Br J Anaesth, 2002. **89**(6): p. 839-45.
463. Drake, R., et al., *Impact of an antiemetic protocol on postoperative nausea and vomiting in children.* Paediatr Anaesth, 2001. **11**(1): p. 85-91.
464. Sandhu, S., et al., *Transient paralysis after administration of a single dose of cyclizine.* Anaesthesia, 2005. **60**(12): p. 1235-6.
465. Walker, R.B., *HPLC analysis and pharmacokinetics of cyclizine.*, 1995, Rhodes University,: Grahamstown South Africa.

466. Kanfer, I. and R. Walker, *Pharmacokinetics of cyclizine after single dose oral administration to human volunteers.*, 1998, Pharmaceutical Science.
467. Krach, L.E., *Pharmacotherapy of spasticity: oral medications and intrathecal baclofen.* J Child Neurol, 2001. **16**(1): p. 31-6.
468. Pinder, R.M., et al., *Dantrolene sodium: a review of its pharmacological properties and therapeutic efficacy in spasticity.* Drugs, 1977. **13**(1): p. 3-23.
469. Dupuis, L.L., R. Lau, and M.L. Greenberg, *Delayed nausea and vomiting in children receiving antineoplastics.* Med Pediatr Oncol, 2001. **37**(2): p. 115-21.
470. de Vries, M.A., et al., *Effect of dexamethasone on quality of life in children with acute lymphoblastic leukaemia: a prospective observational study.* Health Qual Life Outcomes, 2008. **6**(1): p. 103.
471. Tramer, M.R., *[Prevention and treatment of postoperative nausea and vomiting in children. An evidence-based approach].* Ann Fr Anesth Reanim, 2007. **26**(6): p. 529-34.
472. Dupuis, L.L., et al., *Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients.* Pediatric Blood and Cancer, 2013. **60**(7): p. 1073-1082.
473. Hewitt, M., et al., *Opioid use in palliative care of children and young people with cancer.* J Pediatr, 2008. **152**(1): p. 39-44.
474. MHRA, *Ayendi 720 microgram/actuation Nasal Spray and Ayendi 1600 microgram/actuation Nasal Spray (Diamorphine hydrochloride)*, 2014, Medicines and Healthcare products Regulatory Agency.
475. Mathew, A., et al., *The efficacy of diazepam in enhancing motor function in children with spastic cerebral palsy.* J Trop Pediatr, 2005. **51**(2): p. 109-13.
476. O'Dell, C. and K. O'Hara, *School nurses' experience with administration of rectal diazepam gel for seizures.* J Sch Nurs, 2007. **23**(3): p. 166-9.
477. Srivastava, M. and D. Walsh, *Diazepam as an adjuvant analgesic to morphine for pain due to skeletal muscle spasm.* Support Care Cancer, 2003. **11**(1): p. 66-9.
478. MHRA, *Domperidone: small risk of serious ventricular arrhythmia and sudden cardiac death*, 2012. p. A2.
479. Gubbay, A. and K. Langdon, *'Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children'.* Dev Med Child Neurol, 2009. **51**(6): p. 491-2; author reply 492.
480. Heinrich, M., et al., *Self-administered procedural analgesia using nitrous oxide/oxygen (50:50) in the pediatric surgery emergency room: effectiveness and limitations.* Eur J Pediatr Surg, 2015. **25**(3): p. 250-6.
481. Ingelmo, P., A. Wei, and G. Rivera, *Nitrous oxide for procedural analgesia at home in a child with epidermolysis bullosa.* Paediatr Anaesth, 2017. **27**(7): p. 776-778.
482. Novak, P.H., et al., *Acute drug prescribing to children on chronic antiepilepsy therapy and the potential for adverse drug interactions in primary care.* Br J Clin Pharmacol, 2005. **59**(6): p. 712-7.
483. Tsoukas, C., et al., *Evaluation of the efficacy and safety of etoricoxib in the treatment of hemophilic arthropathy.* Blood, 2006. **107**(5): p. 1785-90.
484. Corzo, J.L., et al., *Tolerance to COX-2 inhibitors in children with hypersensitivity to nonsteroidal anti-inflammatory drugs.* Br J Dermatol, 2014. **170**(3): p. 725-9.
485. Grape, S., et al., *Formulations of fentanyl for the management of pain.* Drugs. **70**(1): p. 57-72.

486. Cappelli, C., et al., *[Transdermal Fentanyl: news in oncology.].* Clin Ter, 2008. **159**(4): p. 257-260.
487. Weschules, D.J., et al., *Toward evidence-based prescribing at end of life: a comparative analysis of sustained-release morphine, oxycodone, and transdermal fentanyl, with pain, constipation, and caregiver interaction outcomes in hospice patients.* Pain Med, 2006. **7**(4): p. 320-9.
488. Borland, M., et al., *A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department.* Ann Emerg Med, 2007. **49**(3): p. 335-40.
489. Borland, M.L., I. Jacobs, and G. Geelhoed, *Intranasal fentanyl reduces acute pain in children in the emergency department: a safety and efficacy study.* Emerg Med (Fremantle), 2002. **14**(3): p. 275-80.
490. Drake, R., J. Longworth, and J.J. Collins, *Opioid rotation in children with cancer.* J Palliat Med, 2004. **7**(3): p. 419-22.
491. Friedrichsdorf, S.J. and T.I. Kang, *The management of pain in children with life-limiting illnesses.* Pediatr Clin North Am, 2007. **54**(5): p. 645-72, x.
492. Hunt, A., et al., *Transdermal fentanyl for pain relief in a paediatric palliative care population.* Palliat Med, 2001. **15**(5): p. 405-12.
493. Kanowitz, A., et al., *Safety and effectiveness of fentanyl administration for prehospital pain management.* Prehosp Emerg Care, 2006. **10**(1): p. 1-7.
494. Mercadante, S., et al., *Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain.* Br J Cancer, 2007. **96**(12): p. 1828-33.
495. Noyes, M. and H. Irving, *The use of transdermal fentanyl in pediatric oncology palliative care.* Am J Hosp Palliat Care, 2001. **18**(6): p. 411-6.
496. Weschules, D.J., et al., *Are newer, more expensive pharmacotherapy options associated with superior symptom control compared to less costly agents used in a collaborative practice setting?* Am J Hosp Palliat Care, 2006. **23**(2): p. 135-49.
497. Harlos, M.S., et al., *Intranasal fentanyl in the palliative care of newborns and infants.* J Pain Symptom Manage, 2013. **46**(2): p. 265-74.
498. Mercadante, S., et al., *Fentanyl Pectin Nasal Spray Versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study.* J Pain Symptom Manage, 2016. **52**(1): p. 27-34.
499. Mercadante, S., et al., *Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group.* Support Care Cancer, 2016. **24**(2): p. 961-8.
500. Tobias, J.D., *Subcutaneous administration of fentanyl and midazolam to prevent withdrawal after prolonged sedation in children.* Crit Care Med, 1999. **27**(10): p. 2262-5.
501. Hunt, R., et al., *A comparison of subcutaneous morphine and fentanyl in hospice cancer patients.* J Pain Symptom Manage, 1999. **18**(2): p. 111-9.
502. McNair, C., B. Graydon, and A. Taddio, *A cohort study of intranasal fentanyl for procedural pain management in neonates.* Paediatr Child Health, 2018. **23**(8): p. e170-e175.
503. Oshikoya, K.A., et al., *Serious Adverse Events Associated with Off-Label Use of Azithromycin or Fentanyl in Children in Intensive Care Units: A Retrospective Chart Review.* Paediatr Drugs, 2019. **21**(1): p. 47-58.
504. Setlur, A. and H. Friedland, *Treatment of pain with intranasal fentanyl in pediatric patients in an acute care setting: a systematic review.* Pain Manag, 2018. **8**(5): p. 341-352.

505. Pieper, L., J. Wager, and B. Zernikow, *Intranasal fentanyl for respiratory distress in children and adolescents with life-limiting conditions.* BMC Palliat Care, 2018. **17**(1): p. 106.
506. Lim, S.Y., et al., *Dosing for Fentanyl Infusion in Obese Children: Just Because It's What We Have Always Done Doesn't Mean It Is Right.* J Pediatr Pharmacol Ther, 2018. **23**(3): p. 223-226.
507. Coombes, L., K. Burke, and A.K. Anderson, *The use of rapid onset fentanyl in children and young people for breakthrough cancer pain.* Scand J Pain, 2017. **17**: p. 256-259.
508. Fein, D.M., et al., *Intranasal fentanyl for initial treatment of vaso-occlusive crisis in sickle cell disease.* Pediatr Blood Cancer, 2017. **64**(6).
509. Pienaar, E.D., T. Young, and H. Holmes, *Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children.* Cochrane Database Syst Rev, 2006. **3**: p. CD003940.
510. Pfizer. *DIFLUCAN U.S. Physician Prescribing Information* 2014; Available from: http://www.pfizer.com/products/product-detail/diflucan.
511. Hetrick, S., et al., *Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents.* Cochrane Database Syst Rev, 2007(3): p. CD004851.
512. Millet, B., et al., *Obsessive-compulsive disorder: evaluation of clinical and biological circadian parameters during fluoxetine treatment.* Psychopharmacology (Berl), 1999. **146**(3): p. 268-74.
513. Monteleone, P., et al., *Plasma melatonin and cortisol circadian patterns in patients with obsessive-compulsive disorder before and after fluoxetine treatment.* Psychoneuroendocrinology, 1995. **20**(7): p. 763-70.
514. Roth, D., et al., *Depressing research.* Lancet, 2004. **363**(9426): p. 2087.
515. Whittington, C.J., et al., *Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data.* Lancet, 2004. **363**(9418): p. 1341-5.
516. Caraceni, A., et al., *Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.* J Clin Oncol, 2004. **22**(14): p. 2909-17.
517. Butkovic, D., S. Toljan, and B. Mihovilovic-Novak, *Experience with gabapentin for neuropathic pain in adolescents: report of five cases.* Paediatr Anaesth, 2006. **16**(3): p. 325-9.
518. Pfizer. *NEURONTIN U.S. Physician Prescribing Information*. 2014; Available from: http://www.pfizer.com/products/product-detail/neurontin.
519. van den Beuken-van Everdingen, M.H., et al., *Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review.* Pain Pract, 2016.
520. Siemens, W., et al., *Drug treatments for pruritus in adult palliative care.* Dtsch Arztebl Int, 2014. **111**(50): p. 863-70.
521. www.palliativedrugs.com, 2016.
522. Edwards, L., et al., *Gabapentin Use in the Neonatal Intensive Care Unit.* J Pediatr, 2016. **169**: p. 310-2.
523. Hauer, J.M. and J.C. Solodiuk, *Gabapentin for management of recurrent pain in 22 nonverbal children with severe neurological impairment: a retrospective analysis.* J Palliat Med, 2015. **18**(5): p. 453-6.
524. Hauer, J.M., B.S. Wical, and L. Charnas, *Gabapentin successfully manages chronic unexplained irritability in children with severe neurologic impairment.* Pediatrics, 2007. **119**(2): p. e519-22.
525. Allegaert, K. and G. Naulaers, *Gabapentin as part of multimodal analgesia in a newborn with epidermolysis bullosa.* Paediatr Anaesth, 2010. **20**(10): p. 972-3.

526. Behm, M.O. and G.L. Kearns, *Treatment of pain with gabapentin in a neonate.* Pediatrics, 2001. **108**(2): p. 482-4.
527. Hauer, J. and D. Mackey, *Treatment with gabapentin associated with resolution of apnea in two infants with neurologic impairment.* J Palliat Med, 2013. **16**(4): p. 455-8.
528. (NICE), N.I.o.C.E. *The epilepsies: the diagnosis and management of the epilepsies in children and young people in primary and secondary care - Quick reference guide*. 2004; Available from: http://www.nice.org.uk/pdf/CG020childrenquickrefguide.pdf.
529. PHE and NHSE, *Advice for prescribers on the risk of the misuse of pregabalin and gabapentin* GOV.UK, Editor 2014.
530. Lumsden, D.E., et al., *Pharmacological management of abnormal tone and movement in cerebral palsy.* Arch Dis Child, 2019.
531. Fehlings, D., et al., *Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review.* Dev Med Child Neurol, 2018. **60**(4): p. 356-366.
532. Brown, S., et al., *A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children.* Scand J Pain, 2016. **13**: p. 156-163.
533. Cooper, T.E., et al., *Antidepressants for chronic non-cancer pain in children and adolescents.* Cochrane Database Syst Rev, 2017. **8**: p. CD012535.
534. EMC. *https://www.medicines.org.uk/emc/product/5003/smpc*
535. MedicinesComplete, *https://www.medicinescomplete.com/mc/alerts/current/alert00005640.htm?q=gabapentin&t=search&ss=text&tot=49&p=6#_hit*
536. PharmacyTimes, *https://www.pharmacytimes.com/contributor/jeffrey-fudin/2015/09/how-gabapentin-differs-from-pregabalin,*.
537. Back, I.N., et al., *A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle.* Palliat Med, 2001. **15**(4): p. 329-36.
538. Bennett, M., et al., *Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care.* Palliat Med, 2002. **16**(5): p. 369-74.
539. Dumortier, G., et al., *[Prescription of psychotropic drugs in paediatry: approved indications and therapeutic perspectives].* Encephale, 2005. **31**(4 Pt 1): p. 477-89.
540. Breitbart, W., et al., *A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients.* Am J Psychiatry, 1996. **153**(2): p. 231-7.
541. Breitbart, W. and D. Strout, *Delirium in the terminally ill.* Clin Geriatr Med, 2000. **16**(2): p. 357-72.
542. Negro, S., et al., *Physical compatibility and in vivo evaluation of drug mixtures for subcutaneous infusion to cancer patients in palliative care.* Support Care Cancer, 2002. **10**(1): p. 65-70.
543. Saito, T. and S. Shinno, *[How we have treated and cared patients with Duchenne muscular dystrophy and severe congestive heart failure].* No To Hattatsu, 2005. **37**(4): p. 281-6.
544. Murray-Brown, F. and S. Dorman, *Haloperidol for the treatment of nausea and vomiting in palliative care patients.* Cochrane Database Syst Rev, 2015(11): p. CD006271.
545. Masman, A.D., et al., *Medication use during end-of-life care in a palliative care centre.* Int J Clin Pharm, 2015. **37**(5): p. 767-75.
546. Goncalves, F., A. Almeida, and S. Pereira, *A Protocol for the Control of Agitation in Palliative Care.* Am J Hosp Palliat Care, 2015.
547. Hodgins, G.E., et al., *Steroid-Induced Psychosis in the Pediatric Population: A New Case and Review of the Literature.* J Child Adolesc Psychopharmacol, 2018. **28**(5): p. 354-359.

548. Sagreiya, H., et al., *Differences in Antipsychotic-Related Adverse Events in Adult, Pediatric, and Geriatric Populations.* Cureus, 2017. **9**(2): p. e1059.
549. Bell, R.F., et al., *Controlled clinical trials in cancer pain. How controlled should they be? A qualitative systematic review.* Br J Cancer, 2006.
550. Quigley, C. and P. Wiffen, *A systematic review of hydromorphone in acute and chronic pain.* J Pain Symptom Manage, 2003. **25**(2): p. 169-78.
551. Bosilkovska, M., et al., *Analgesics in patients with hepatic impairment: pharmacology and clinical implications.* Drugs, 2012. **72**(12): p. 1645-69.
552. Busse, J., L. Phillips, and W. Schechter, *Long-Term Intravenous Ketamine for Analgesia in a Child with Severe Chronic Intestinal Graft versus Host Disease.* Case Rep Anesthesiol, 2015. **2015**: p. 834168.
553. Wang, L., et al., *Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials.* Can J Anaesth, 2016. **63**(3): p. 311-25.
554. Reddy, A., et al., *The Conversion Ratio From Intravenous Hydromorphone to Oral Opioids in Cancer Patients.* J Pain Symptom Manage, 2017. **54**(3): p. 280-288.
555. Tytgat, G.N., *Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain.* Drugs, 2007. **67**(9): p. 1343-57.
556. Herxheimer, A. and A.C. de Groot, *Some effects of injected hyoscine butylbromide: a versatile class experiment in human pharmacology.* Br J Clin Pharmacol, 1977. **4**(3): p. 337-42.
557. Herxheimer, A. and J.J. Misiewicz, *Oral hyoscine butylbromide for irritable bowel syndrome?* Br Med J, 1979. **1**(6165): p. 752.
558. NICE, *Care of dying adults in the last days of life*, 2015.
559. Mercadante, S., et al., *Hyoscine Butylbromide for the Management of Death Rattle: Sooner Rather Than Later.* J Pain Symptom Manage, 2018. **56**(6): p. 902-907.
560. MRHA. *Hyoscine butylbromide (Buscopan) injection: risk of serious adverse effects in patients with underlying cardiac disease*. 2017; Available from: https://www.gov.uk/drug-safety-update/hyoscine-butylbromide-buscopan-injection-risk-of-serious-adverse-effects-in-patients-with-underlying-cardiac-disease.
561. Titchen, T., N. Cranswick, and S. Beggs, *Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital.* Br J Clin Pharmacol, 2005. **59**(6): p. 718-23.
562. NICE Clinical Guideline. *Feverish illness in children. CG160.* . 2013; May [Available from: http://guidance.nice.org.uk/CG160.
563. NICE, *Non-steroidal anti-inflammatory drugs*, 2015.
564. Chlud, K. and H. Wagener, *Percutaneous nonsteroidal anti-inflammatory drug (NSAID) therapy with particular reference to pharmacokinetic factors.* EULAR Bulletin, 1987(2): p. 40-43.
565. Poonai, N., et al., *Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial.* CMAJ, 2017. **189**(40): p. E1252-E1258.
566. Castro-Rodriguez, J.A., J.R. G, and E.R.-M. C, *Principal findings of systematic reviews of acute asthma treatment in childhood.* J Asthma, 2015. **52**(10): p. 1038-45.
567. Calderon, J., E. Rubin, and W.L. Sobota, *Potential use of ipatropium bromide for the treatment of clozapine-induced hypersalivation: a preliminary report.* Int Clin Psychopharmacol, 2000. **15**(1): p. 49-52.

568. Anderson, B.J. and G.M. Palmer, *Recent developments in the pharmacological management of pain in children.* Curr Opin Anaesthesiol, 2006. **19**(3): p. 285-92.
569. Anghelescu, D.L. and L.L. Oakes, *Ketamine use for reduction of opioid tolerance in a 5-year-old girl with end-stage abdominal neuroblastoma.* J Pain Symptom Manage, 2005. **30**(1): p. 1-3.
570. Campbell-Fleming, J.M. and A. Williams, *The use of ketamine as adjuvant therapy to control severe pain.* Clin J Oncol Nurs, 2008. **12**(1): p. 102-7.
571. Legge, J., N. Ball, and D.P. Elliott, *The potential role of ketamine in hospice analgesia: a literature review.* Consult Pharm, 2006. **21**(1): p. 51-7.
572. Tsui, B.C., et al., *Intravenous ketamine infusion as an adjuvant to morphine in a 2-year-old with severe cancer pain from metastatic neuroblastoma.* J Pediatr Hematol Oncol, 2004. **26**(10): p. 678-80.
573. Fitzgibbon, E.J., et al., *Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine.* J Pain Symptom Manage, 2002. **23**(2): p. 165-70.
574. Benitez-Rosario, M.A., et al., *A strategy for conversion from subcutaneous to oral ketamine in cancer pain patients: effect of a 1:1 ratio.* J Pain Symptom Manage, 2011. **41**(6): p. 1098-105.
575. Bell, R.F., C. Eccleston, and E.A. Kalso, *Ketamine as an adjuvant to opioids for cancer pain.* Cochrane Database Syst Rev, 2012. **11**: p. CD003351.
576. Bredlau, A.L., et al., *Oral ketamine for children with chronic pain: a pilot phase 1 study.* J Pediatr, 2013. **163**(1): p. 194-200 e1.
577. Downing, J., et al., *Pediatric pain management in palliative care.* Pain Manag, 2015. **5**(1): p. 23-35.
578. Graudins, A., et al., *The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries.* Ann Emerg Med, 2015. **65**(3): p. 248-254 e1.
579. Roelofse, J.A., *The evolution of ketamine applications in children.* Paediatr Anaesth, 2010. **20**(3): p. 240-5.
580. Niesters, M., C. Martini, and A. Dahan, *Ketamine for chronic pain: risks and benefits.* Br J Clin Pharmacol, 2014. **77**(2): p. 357-67.
581. Morgan, C.J., H.V. Curran, and D. Independent Scientific Committee on, *Ketamine use: a review.* Addiction, 2012. **107**(1): p. 27-38.
582. Morgan, C.J., L. Muetzelfeldt, and H.V. Curran, *Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study.* Addiction, 2010. **105**(1): p. 121-33.
583. Mitchell, A.C., *Generalized hyperalgesia and allodynia following abrupt cessation of subcutaneous ketamine infusion.* Palliat Med, 1999. **13**(5): p. 427-8.
584. Golub, D., et al., *Potential consequences of high-dose infusion of ketamine for refractory status epilepticus: case reports and systematic literature review.* Anaesth Intensive Care, 2018. **46**(5): p. 516-528.
585. Cullen, K.R., et al., *Intravenous Ketamine for Adolescents with Treatment-Resistant Depression: An Open-Label Study.* J Child Adolesc Psychopharmacol, 2018. **28**(7): p. 437-444.
586. Majidi, S., et al., *Onset and Effect Duration of Intrabuccal Space and Intramuscular Ketamine in Pediatrics.* Adv Biomed Res, 2018. **7**: p. 91.
587. Aldrink, J.H., et al., *Safety of ketorolac in surgical neonates and infants 0 to 3 months old.* J Pediatr Surg, 2011. **46**(6): p. 1081-5.

588. Cohen, M.N., et al., *Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months.* Anesth Analg, 2011. **112**(3): p. 655-60.
589. Zuppa, A.F., et al., *Population pharmacokinetics of ketorolac in neonates and young infants.* Am J Ther, 2009. **16**(2): p. 143-6.
590. Hong, J.Y., et al., *Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children.* J Urol, 2010. **183**(4): p. 1551-5.
591. Jo, Y.Y., et al., *Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy.* Acta Anaesthesiol Scand, 2011. **55**(1): p. 54-9.
592. Keidan, I., et al., *Intraoperative ketorolac is an effective substitute for fentanyl in children undergoing outpatient adenotonsillectomy.* Paediatr Anaesth, 2004. **14**(4): p. 318-23.
593. Moreno, M., F.J. Castejon, and M.A. Palacio, *Patient-controlled analgesia with ketorolac in pediatric surgery.* J Physiol Biochem, 2000. **56**(3): p. 209-16.
594. Shende, D. and K. Das, *Comparative effects of intravenous ketorolac and pethidine on perioperative analgesia and postoperative nausea and vomiting (PONV) for paediatric strabismus surgery.* Acta Anaesthesiol Scand, 1999. **43**(3): p. 265-9.
595. Chiaretti, A., et al., *[Analgesic efficacy of ketorolac and fentanyl in pediatric intensive care].* Pediatr Med Chir, 1997. **19**(6): p. 419-24.
596. Forrest, J.B., E.L. Heitlinger, and S. Revell, *Ketorolac for postoperative pain management in children.* Drug Saf, 1997. **16**(5): p. 309-29.
597. Gillis, J.C. and R.N. Brogden, *Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management.* Drugs, 1997. **53**(1): p. 139-88.
598. Neri, E., et al., *Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial.* Arch Dis Child, 2013. **98**(9): p. 721-4.
599. Cozzi, G., et al., *Administering analgesia sublingually is a suitable option for children with acute abdominal pain in the emergency department.* Acta Paediatr, 2019. **108**(1): p. 143-148.
600. Urganci, N., B. Akyildiz, and T.B. Polat, *A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation.* Pediatr Int, 2005. **47**(1): p. 15-9.
601. Lee-Robichaud, H., et al., *Lactulose versus Polyethylene Glycol for Chronic Constipation.* Cochrane Database Syst Rev, 2010(7): p. CD007570.
602. Chen, S.L., et al., *Efficacy and complications of polyethylene glycols for treatment of constipation in children: a meta-analysis.* Medicine (Baltimore), 2014. **93**(16): p. e65.
603. Wirz, S., et al., *Laxative management in ambulatory cancer patients on opioid therapy: a prospective, open-label investigation of polyethylene glycol, sodium picosulphate and lactulose.* Eur J Cancer Care (Engl), 2012. **21**(1): p. 131-40.
604. Orenstein, S.R., et al., *Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease.* J Pediatr, 2009. **154**(4): p. 514-520 e4.
605. Khoshoo, V. and P. Dhume, *Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux.* J Pediatr Gastroenterol Nutr, 2008. **46**(3): p. 352-4.
606. Gremse, D., et al., *Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S319-26.
607. Tolia, V., et al., *Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S308-18.

608. Tolia, V., et al., *Safety of lansoprazole in the treatment of gastroesophageal reflux disease in children.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S300-7.
609. Heyman, M.B., et al., *Pharmacokinetics and pharmacodynamics of lansoprazole in children 13 to 24 months old with gastroesophageal reflux disease.* J Pediatr Gastroenterol Nutr, 2007. **44**(1): p. 35-40.
610. Tran, A., et al., *Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children.* Clin Pharmacol Ther, 2002. **71**(5): p. 359-67.
611. Gunasekaran, T., et al., *Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability.* J Pediatr Gastroenterol Nutr, 2002. **35 Suppl 4**: p. S327-35.
612. Zhang, W., et al., *Age-dependent pharmacokinetics of lansoprazole in neonates and infants.* Paediatr Drugs, 2008. **10**(4): p. 265-74.
613. Springer, M., et al., *Safety and pharmacodynamics of lansoprazole in patients with gastroesophageal reflux disease aged <1 year.* Paediatr Drugs, 2008. **10**(4): p. 255-63.
614. Franco, M.T., et al., *Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood.* Dig Liver Dis, 2000. **32**(8): p. 660-6.
615. Faure, C., et al., *Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis.* Aliment Pharmacol Ther, 2001. **15**(9): p. 1397-402.
616. Litalien, C., Y. Theoret, and C. Faure, *Pharmacokinetics of proton pump inhibitors in children.* Clin Pharmacokinet, 2005. **44**(5): p. 441-66.
617. Messaouik, D., et al., *Comparative study and optimisation of the administration mode of three proton pump inhibitors by nasogastric tube.* Int J Pharm, 2005. **299**(1-2): p. 65-72.
618. Remi, C., et al., *Continuous subcutaneous use of levetiracetam: a retrospective review of tolerability and clinical effects.* J Pain Palliat Care Pharmacother, 2014. **28**(4): p. 371-7.
619. Kim, J.S., et al., *Effectiveness of intravenous levetiracetam as an adjunctive treatment in pediatric refractory status epilepticus.* Pediatr Emerg Care, 2014. **30**(8): p. 525-8.
620. Lyttle, M.D., et al., *Emergency treatment with levetiracetam or phenytoin in status epilepticus in children-the EcLiPSE study: study protocol for a randomised controlled trial.* Trials, 2017. **18**(1): p. 283.
621. Dalziel, S.R., et al., *A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study.* BMC Pediatr, 2017. **17**(1): p. 152.
622. O'Neill, J. and A. Fountain, *Levomepromazine (methotrimeprazine) and the last 48 hours.* Hosp Med, 1999. **60**(8): p. 564-7.
623. Hohl, C.M., et al., *Methotrimeprazine for the management of end-of-life symptoms in infants and children.* J Palliat Care, 2013. **29**(3): p. 178-85.
624. Hans, G., et al., *Management of neuropathic pain after surgical and non-surgical trauma with lidocaine 5% patches: study of 40 consecutive cases.* Curr Med Res Opin, 2009. **25**(11): p. 2737-43.
625. Garnock-Jones, K.P. and G.M. Keating, *Lidocaine 5% medicated plaster: a review of its use in postherpetic neuralgia.* Drugs, 2009. **69**(15): p. 2149-65.
626. *Lidocaine plasters for postherpetic neuralgia?* Drug Ther Bull, 2008. **46**(2): p. 14-6.
627. Binder, A., et al., *Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial.* Clin Drug Investig, 2009. **29**(6): p. 393-408.

628. Hans, G., et al., *Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study.* Curr Med Res Opin, 2009. **25**(5): p. 1295-305.
629. Nalamachu, S., et al., *Influence of anatomic location of lidocaine patch 5% on effectiveness and tolerability for postherpetic neuralgia.* Patient Prefer Adherence, 2013. **7**: p. 551-7.
630. Goddard, J.M. and R.L. Reaney, *Lidocaine 5%-medicated plaster (Versatis) for localised neuropathic pain: results of a multicentre evaluation of use in children and adolescents.* Br J Pain, 2018. **12**(3): p. 189-193.
631. Sommer, C. and G. Cruccu, *Topical Treatment of Peripheral Neuropathic Pain: Applying the Evidence.* J Pain Symptom Manage, 2017. **53**(3): p. 614-629.
632. Karan, S., *Lomotil in diarrhoeal illnesses.* Arch Dis Child, 1979. **54**(12): p. 984.
633. Bala, K., S.S. Khandpur, and V.V. Gujral, *Evaluation of efficacy and safety of lomotil in acute diarrhoeas in children.* Indian Pediatr, 1979. **16**(10): p. 903-7.
634. Waterston, A.J., *Lomotil in diarrhoeal illnesses.* Arch Dis Child, 1980. **55**(7): p. 577-8.
635. McCarron, M.M., K.R. Challoner, and G.A. Thompson, *Diphenoxylate-atropine (Lomotil) overdose in children: an update (report of eight cases and review of the literature).* Pediatrics, 1991. **87**(5): p. 694-700.
636. Li, S.T., D.C. Grossman, and P. Cummings, *Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis.* PLoS Med, 2007. **4**(3): p. e98.
637. Kaplan, M.A., et al., *A multicenter randomized controlled trial of a liquid loperamide product versus placebo in the treatment of acute diarrhea in children.* Clin Pediatr (Phila), 1999. **38**(10): p. 579-91.
638. Omar, M.I. and C.E. Alexander, *Drug treatment for faecal incontinence in adults.* Cochrane Database Syst Rev, 2013. **6**: p. CD002116.
639. Burtles, R. and B. Astley, *Lorazepam in children. A double-blind trial comparing lorazepam, diazepam, trimeprazine and placebo.* Br J Anaesth, 1983. **55**(4): p. 275-9.
640. Hanson, S. and N. Bansal, *The clinical effectiveness of Movicol in children with severe constipation: an outcome audit.* Paediatr Nurs, 2006. **18**(2): p. 24-8.
641. Braam, W., et al., *Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study.* J Intellect Disabil Res, 2008. **52**(Pt 3): p. 256-64.
642. Andersen, I.M., et al., *Melatonin for insomnia in children with autism spectrum disorders.* J Child Neurol, 2008. **23**(5): p. 482-5.
643. Guerrero, J.M., et al., *Impairment of the melatonin rhythm in children with Sanfilippo syndrome.* J Pineal Res, 2006. **40**(2): p. 192-3.
644. Gupta, R. and J. Hutchins, *Melatonin: a panacea for desperate parents? (Hype or truth).* Arch Dis Child, 2005. **90**(9): p. 986-7.
645. Ivanenko, A., et al., *Melatonin in children and adolescents with insomnia: a retrospective study.* Clin Pediatr (Phila), 2003. **42**(1): p. 51-8.
646. Mariotti, P., et al., *Sleep disorders in Sanfilippo syndrome: a polygraphic study.* Clin Electroencephalogr, 2003. **34**(1): p. 18-22.
647. Masters, K.J., *Melatonin for sleep problems.* J Am Acad Child Adolesc Psychiatry, 1996. **35**(6): p. 704.
648. Owens, J.A., C.L. Rosen, and J.A. Mindell, *Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians.* Pediatrics, 2003. **111**(5 Pt 1): p. e628-35.

649. Paavonen, E.J., et al., *Effectiveness of melatonin in the treatment of sleep disturbances in children with Asperger disorder.* J Child Adolesc Psychopharmacol, 2003. **13**(1): p. 83-95.
650. Smits, M.G., et al., *Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial.* J Child Neurol, 2001. **16**(2): p. 86-92.
651. Smits, M.G., et al., *Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial.* J Am Acad Child Adolesc Psychiatry, 2003. **42**(11): p. 1286-93.
652. van der Heijden, K.B., et al., *Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia.* J Sleep Res, 2005. **14**(2): p. 187-94.
653. Van der Heijden, K.B., et al., *Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia.* J Am Acad Child Adolesc Psychiatry, 2007. **46**(2): p. 233-41.
654. Wasdell, M.B., et al., *A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities.* J Pineal Res, 2008. **44**(1): p. 57-64.
655. Zhdanova, I.V., *Melatonin as a hypnotic: pro.* Sleep Med Rev, 2005. **9**(1): p. 51-65.
656. Zucconi, M. and O. Bruni, *Sleep disorders in children with neurologic diseases.* Semin Pediatr Neurol, 2001. **8**(4): p. 258-75.
657. Gringras, P., et al., *Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial.* BMJ, 2012. **345**: p. e6664.
658. Ferracioli-Oda, E., A. Qawasmi, and M.H. Bloch, *Meta-analysis: melatonin for the treatment of primary sleep disorders.* PLoS One, 2013. **8**(5): p. e63773.
659. Moksnes, K., et al., *How to switch from morphine or oxycodone to methadone in cancer patients? a randomised clinical phase II trial.* Eur J Cancer, 2011. **47**(16): p. 2463-70.
660. Poulain, P., et al., *Efficacy and Safety of Two Methadone Titration Methods for the Treatment of Cancer-Related Pain: The EQUIMETH2 Trial (Methadone for Cancer-Related Pain).* J Pain Symptom Manage, 2016. **52**(5): p. 626-636 e1.
661. Ripamonti, C., et al., *Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio?* J Clin Oncol, 1998. **16**(10): p. 3216-21.
662. Ayonrinde, O.T. and D.T. Bridge, *The rediscovery of methadone for cancer pain management.* Med J Aust, 2000. **173**(10): p. 536-40.
663. Benitez-Rosario, M.A., et al., *Morphine-methadone opioid rotation in cancer patients: analysis of dose ratio predicting factors.* J Pain Symptom Manage, 2009. **37**(6): p. 1061-8.
664. Bruera, E., et al., *Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study.* J Clin Oncol, 2004. **22**(1): p. 185-92.
665. Berens, R.J., et al., *A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients.* Anesth Analg, 2006. **102**(4): p. 1045-50.
666. Colvin, L., K. Forbes, and M. Fallon, *Difficult pain.* Bmj, 2006. **332**(7549): p. 1081-3.
667. Dale, O., P. Sheffels, and E.D. Kharasch, *Bioavailabilities of rectal and oral methadone in healthy subjects.* Br J Clin Pharmacol, 2004. **58**(2): p. 156-62.
668. Davies, D., D. DeVlaming, and C. Haines, *Methadone analgesia for children with advanced cancer.* Pediatr Blood Cancer, 2008. **51**(3): p. 393-7.
669. Ripamonti, C. and M. Bianchi, *The use of methadone for cancer pain.* Hematol Oncol Clin North Am, 2002. **16**(3): p. 543-55.
670. Weschules, D.J. and K.T. Bain, *A systematic review of opioid conversion ratios used with methadone for the treatment of pain.* Pain Med, 2008. **9**(5): p. 595-612.

671. Weschules, D.J., et al., *Methadone and the hospice patient: prescribing trends in the home-care setting.* Pain Med, 2003. **4**(3): p. 269-76.
672. Heppe, D.B., M.C. Haigney, and M.J. Krantz, *The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study.* J Palliat Med. **13**(6): p. 638-9.
673. Mercadante, S., P. Ferrera, and E. Arcuri, *The use of fentanyl buccal tablets as breakthrough medication in patients receiving chronic methadone therapy: an open label preliminary study.* Support Care Cancer.
674. Mercadante, S., et al., *Changes of QTc interval after opioid switching to oral methadone.* Support Care Cancer, 2013. **21**(12): p. 3421-4.
675. Habashy, C., et al., *Methadone for Pain Management in Children with Cancer.* Paediatr Drugs, 2018. **20**(5): p. 409-416.
676. Madden, K., et al., *The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain.* Pediatr Blood Cancer, 2017. **64**(11).
677. Ray, W.A., et al., *Out-of-hospital mortality among patients receiving methadone for noncancer pain.* JAMA Intern Med, 2015. **175**(3): p. 420-7.
678. Fife, A., et al., *Methadone conversion in infants and children: Retrospective cohort study of 199 pediatric inpatients.* J Opioid Manag, 2016. **12**(2): p. 123-30.
679. Rodriques A et al, *Methylnaltrexone for Opiod-Induced Constipation in Pediatric Oncology Patients. Pediatr Blood Cancer.* Pediatr Blood Cancer, 2013. **Jun1**(4).
680. Laubisch, J.E. and J.N. Baker, *Methylnaltrexone use in a seventeen-month-old female with progressive cancer and rectal prolapse.* J Palliat Med, 2013. **16**(11): p. 1486-8.
681. Garten, L. and C. Buhrer, *Reversal of morphine-induced urinary retention after methylnaltrexone.* Arch Dis Child Fetal Neonatal Ed, 2012. **97**(2): p. F151-3.
682. Garten, L., P. Degenhardt, and C. Buhrer, *Resolution of opioid-induced postoperative ileus in a newborn infant after methylnaltrexone.* J Pediatr Surg, 2011. **46**(3): p. e13-5.
683. Kissling, K.T., L.R. Mohassel, and J. Heintz, *Methylnaltrexone for opioid-induced constipation in a pediatric oncology patient.* J Pain Symptom Manage, 2012. **44**(1): p. e1-3.
684. Lee, J.M. and J. Mooney, *Methylnaltrexone in treatment of opioid-induced constipation in a pediatric patient.* Clin J Pain, 2012. **28**(4): p. 338-41.
685. Madanagopolan, N., *Metoclopramide in hiccup.* Curr Med Res Opin, 1975. **3**(6): p. 371-4.
686. Alhashimi, D., H. Alhashimi, and Z. Fedorowicz, *Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents.* Cochrane Database Syst Rev, 2006. **3**: p. CD005506.
687. Yis, U., et al., *Metoclopramide induced dystonia in children: two case reports.* Eur J Emerg Med, 2005. **12**(3): p. 117-9.
688. EMA, *European Medicines Agency recommends changes to the use of metoclopramide*, 2013.
689. Trindade, L.C., et al., *Evaluation of topical metronidazole in the healing wounds process: an experimental study.* Rev Col Bras Cir, 2010. **37**(5): p. 358-63.
690. Castro, V.d., *Odor management in fungating wounds with metronidazole: a systematic review.* JHPN, 2015. **17**(1): p. 73-79.
691. Collins, C.D., S. Cookinham, and J. Smith, *Management of oropharyngeal candidiasis with localized oral miconazole therapy: efficacy, safety, and patient acceptability.* Patient Prefer Adherence, 2011. **5**: p. 369-74.
692. De Pauw, A. and T. De Backer, *Miconazole buccal gel and risk for systemic bleeding: how certain topical formula can interfere with anticoagulants.* Acta Clin Belg, 2015. **70**(2): p. 121-3.

693. Lalla, R.V. and R.J. Bensadoun, *Miconazole mucoadhesive tablet for oropharyngeal candidiasis.* Expert Rev Anti Infect Ther, 2011. **9**(1): p. 13-7.
694. Castro Conde, J.R., et al., *Midazolam in neonatal seizures with no response to phenobarbital.* Neurology, 2005. **64**(5): p. 876-9.
695. Harte, G.J., et al., *Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates.* J Paediatr Child Health, 1997. **33**(4): p. 335-8.
696. Lee, T.C., et al., *Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation: midazolam neonatal pharmacokinetics.* Anesthesiology, 1999. **90**(2): p. 451-7.
697. Hu, K.C., et al., *Continuous midazolam infusion in the treatment of uncontrollable neonatal seizures.* Acta Paediatr Taiwan, 2003. **44**(5): p. 279-81.
698. Burger, B. *Paradoxical Reactions from Benzodiazepines – A Review of the Literature*. Society for Pediatric Sedation, 2014. **3**.
699. Berde, C.B. and N.F. Sethna, *Drug therapy - Analgesics for the treatment of pain in children.* New England Journal of Medicine, 2002. **347**(14): p. 1094-1103.
700. Boyle, E.M., et al., *Assessment of persistent pain or distress and adequacy of analgesia in preterm ventilated infants.* Pain, 2006. **124**(1-2): p. 87-91.
701. Cohen, S.P. and T.C. Dawson, *Nebulized morphine as a treatment for dyspnea in a child with cystic fibrosis.* Pediatrics, 2002. **110**(3): p. e38.
702. Dougherty, M. and M.R. DeBaun, *Rapid increase of morphine and benzodiazepine usage in the last three days of life in children with cancer is related to neuropathic pain.* J Pediatr, 2003. **142**(4): p. 373-6.
703. Flogegard, H. and G. Ljungman, *Characteristics and adequacy of intravenous morphine infusions in children in a paediatric oncology setting.* Med Pediatr Oncol, 2003. **40**(4): p. 233-8.
704. Hain, R.D., et al., *Strong opioids in pediatric palliative medicine.* Paediatr Drugs, 2005. **7**(1): p. 1-9.
705. Hall, R.W., et al., *Morphine, Hypotension, and Adverse Outcomes Among Preterm Neonates: Who's to Blame? Secondary Results From the NEOPAIN Trial.* Pediatrics, 2005. **115**(5): p. 1351-1359.
706. Lundeberg, S., et al., *Perception of pain following rectal administration of morphine in children: a comparison of a gel and a solution.* Paediatr Anaesth, 2006. **16**(2): p. 164-9.
707. Miser, A.W., et al., *Continuous subcutaneous infusion of morphine in children with cancer.* Am J Dis Child, 1983. **137**(4): p. 383-5.
708. Nahata, M.C., et al., *Analgesic plasma concentrations of morphine in children with terminal malignancy receiving a continuous subcutaneous infusion of morphine sulfate to control severe pain.* Pain, 1984. **18**(2): p. 109-14.
709. Sittl, R. and R. Richter, *[Cancer pain therapy in children and adolescents using morphine].* Anaesthesist, 1991. **40**(2): p. 96-9.
710. Van Hulle Vincent, C. and M.J. Denyes, *Relieving children's pain: nurses' abilities and analgesic administration practices.* J Pediatr Nurs, 2004. **19**(1): p. 40-50.
711. Viola, R., et al., *The management of dyspnea in cancer patients: a systematic review.* Support Care Cancer, 2008.
712. Wiffen, P.J. and H.J. McQuay, *Oral morphine for cancer pain.* Cochrane Database Syst Rev, 2007(4): p. CD003868.

713. Zeppetella, G., J. Paul, and M.D. Ribeiro, *Analgesic efficacy of morphine applied topically to painful ulcers.* J Pain Symptom Manage, 2003. **25**(6): p. 555-8.
714. Zernikow, B. and G. Lindena, *Long-acting morphine for pain control in paediatric oncology.* Medical & Pediatric Oncology, 2001. **36**(4): p. 451-458.
715. Zernikow, B., et al., *Paediatric cancer pain management using the WHO analgesic ladder--results of a prospective analysis from 2265 treatment days during a quality improvement study.* Eur J Pain, 2006. **10**(7): p. 587-95.
716. Kaiko, R.F., et al., *The bioavailability of morphine in controlled-release 30-mg tablets per rectum compared with immediate-release 30-mg rectal suppositories and controlled-release 30-mg oral tablets.* Pharmacotherapy, 1992. **12**(2): p. 107-13.
717. Wilkinson, T.J., et al., *Pharmacokinetics and efficacy of rectal versus oral sustained-release morphine in cancer patients.* Cancer Chemother Pharmacol, 1992. **31**(3): p. 251-4.
718. Campbell, W.I., *Rectal controlled-release morphine: plasma levels of morphine and its metabolites following the rectal administration of MST Continus 100 mg.* J Clin Pharm Ther, 1996. **21**(2): p. 65-71.
719. Dalzell, A.M., H. Bartlett, and J.S. Lilleyman, *Nabilone: an alternative antiemetic for cancer chemotherapy.* Arch Dis Child, 1986. **61**(5): p. 502-5.
720. Dupuis, L.L. and P.C. Nathan, *Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children.* Paediatr Drugs, 2003. **5**(9): p. 597-613.
721. Chan, H.S., J.A. Correia, and S.M. MacLeod, *Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial.* Pediatrics, 1987. **79**(6): p. 946-52.
722. Tofil, N.M., et al., *The use of enteral naloxone to treat opioid-induced constipation in a pediatric intensive care unit.* Pediatr Crit Care Med, 2006. **7**(3): p. 252-4.
723. Liu, M. and E. Wittbrodt, *Low-dose oral naloxone reverses opioid-induced constipation and analgesia.* J Pain Symptom Manage, 2002. **23**(1): p. 48-53.
724. Glenny, A.M., et al., *A survey of current practice with regard to oral care for children being treated for cancer.* Eur J Cancer, 2004. **40**(8): p. 1217-24.
725. Twycross R, Wilcock A, and Howard P, *Palliative Care Formulary (PCF 5555555556).* 5th5th5th5th5th5th5th5th5th6th ed. 2014201420142014201420142014201420142017: Nottingham: Palliativedrugs.com Ltd.
726. Sassano-Higgins S et al, *Olanzapine reduces delirium symptoms in the critically ill pediatric patient.* J Pediatr Intensive Care, 2013. **2**(2): p. 49-54.
727. Beckwitt-Turkel S et al, *The diagnosis and management of delirium in infancy.* J Child Adolesc Psychopharmacol, 2013. **23**(5): p. 352-56.
728. Turkel SB et al, *Atypical antipsychotic medications to control symptoms of delirium in children and adolescents.* J Child Adolesc Psychopharmacol, 2012. **22**(2): p. 126-130.
729. Kaneishi, K., M. Kawabata, and T. Morita, *Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction.* J Pain Symptom Manage, 2012. **44**(4): p. 604-7.
730. Passik, S.D., et al., *A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain.* J Pain Symptom Manage, 2002. **23**(6): p. 526-32.
731. Licup, N., *Olanzapine for nausea and vomiting.* Am J Hosp Palliat Care, 2010. **27**(6): p. 432-4.
732. Elsayem, A., et al., *Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study.* J Pain Symptom Manage, 2010. **40**(5): p. 774-82.

733. Jackson KC et al, *Drug therapy for delirium in terminally ill adult patients.* Cochrane Database of Systematic Reviews, 2009.
734. Breitbart, W., A. Tremblay, and C. Gibson, *An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients.* Psychosomatics, 2002. **43**(3): p. 175-82.
735. Khojainova, N., et al., *Olanzapine in the management of cancer pain.* J Pain Symptom Manage, 2002. **23**(4): p. 346-50.
736. Navari, R.M. and M.C. Brenner, *Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial.* Support Care Cancer, 2010. **18**(8): p. 951-6.
737. Chelkeba, L., et al., *Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis.* Pharm Pract (Granada), 2017. **15**(1): p. 877.
738. Cole, J.B., et al., *The Use, Safety, and Efficacy of Olanzapine in a Level I Pediatric Trauma Center Emergency Department Over a 10-Year Period.* Pediatr Emerg Care, 2017.
739. Flank, J., et al., *Olanzapine for prevention of chemotherapy-induced nausea and vomiting in children and adolescents: a multi-center, feasibility study.* Support Care Cancer, 2018. **26**(2): p. 549-555.
740. Navari, R.M., *Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients.* Paediatr Drugs, 2017. **19**(3): p. 213-222.
741. Flank, J., et al., *The safety of olanzapine in young children: a systematic review and meta-analysis.* Drug Saf, 2014. **37**(10): p. 791-804.
742. Flank, J., et al., *Olanzapine for treatment and prevention of acute chemotherapy-induced vomiting in children: a retrospective, multi-center review.* Pediatr Blood Cancer, 2015. **62**(3): p. 496-501.
743. Simpson, T. and J. Ivey, *Pediatric management problems. GERD.* Pediatr Nurs, 2005. **31**(3): p. 214-5.
744. Cohen, S., M. Bueno de Mesquita, and F.B. Mimouni, *Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review.* Br J Clin Pharmacol, 2015. **80**(2): p. 200-8.
745. Illueca, M., et al., *Proton pump inhibitor prescribing patterns in newborns and infants.* J Pediatr Pharmacol Ther, 2014. **19**(4): p. 283-7.
746. Karami, S., et al., *Pharmacokinetic Comparison of Omeprazole Granule and Suspension Forms in Children: A Randomized, Parallel Pilot Trial.* Drug Res (Stuttg), 2016. **66**(3): p. 165-8.
747. Tighe, M., et al., *Pharmacological treatment of children with gastro-oesophageal reflux.* Cochrane Database Syst Rev, 2014(11): p. CD008550.
748. Kyriakides, K., S.K. Hussain, and G.J. Hobbs, *Management of opioid-induced pruritus: a role for 5-HT3 antagonists?* Br J Anaesth, 1999. **82**(3): p. 439-41.
749. MHRA Drug Safety Update. *Ondansetron for intravenous use: dose-dependent QT interval prolongation – new posology.* 2013; July ; 6(12): :[Available from: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON296402.
750. Phillips, R.S., et al., *Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood.* Cochrane Database Syst Rev, 2016. **2**: p. CD007786.
751. Kokki, H., et al., *Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children.* Clin Pharmacokinet, 2006. **45**(7): p. 745-54.
752. Kokki, H., et al., *Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children.* Clin Pharmacokinet, 2004. **43**(9): p. 613-22.

753. Zin, C.S., et al., *A randomized, controlled trial of oxycodone versus placebo in patients with postherpetic neuralgia and painful diabetic neuropathy treated with pregabalin.* J Pain. **11**(5): p. 462-71.
754. Zin, C.S., et al., *An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy.* CNS Drugs, 2008. **22**(5): p. 417-42.
755. Czarnecki, M.L., et al., *Controlled-release oxycodone for the management of pediatric postoperative pain.* J Pain Symptom Manage, 2004. **27**(4): p. 379-86.
756. Behzadi, M., S. Joukar, and A. Beik, *Opioids and Cardiac Arrhythmia: A Literature Review.* Med Princ Pract, 2018. **27**(5): p. 401-414.
757. Meents, J.E., et al., *The opioid oxycodone use-dependently inhibits the cardiac sodium channel NaV 1.5.* Br J Pharmacol, 2018. **175**(14): p. 3007-3020.
758. Fanoe, S., et al., *Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro.* Br J Clin Pharmacol, 2009. **67**(2): p. 172-9.
759. Villa, M.P., et al., *Nocturnal oximetry in infants with cystic fibrosis.* Arch Dis Child, 2001. **84**(1): p. 50-54.
760. Balfour-Lynn, I.M., *Domiciliary oxygen for children.* Pediatr Clin North Am, 2009. **56**(1): p. 275-96, xiii.
761. Cachia, E. and S.H. Ahmedzai, *Breathlessness in cancer patients.* Eur J Cancer, 2008. **44**(8): p. 1116-23.
762. Currow, D.C., et al., *Does palliative home oxygen improve dyspnoea? A consecutive cohort study.* Palliat Med, 2009. **23**(4): p. 309-16.
763. Saugstad, O.D., *Chronic lung disease: oxygen dogma revisited.* Acta Paediatr, 2001. **90**(2): p. 113-5.
764. Ross, J.R., et al., *A systematic review of the role of bisphosphonates in metastatic disease.* Health Technol Assess, 2004. **8**(4): p. 1-176.
765. Howe, W., E. Davis, and J. Valentine, *Pamidronate improves pain, wellbeing, fracture rate and bone density in 14 children and adolescents with chronic neurological conditions.* Dev Neurorehabil, 2010. **13**(1): p. 31-6.
766. Wagner, S., et al., *Tolerance and effectiveness on pain control of Pamidronate(R) intravenous infusions in children with neuromuscular disorders.* Ann Phys Rehabil Med, 2011. **54**(6): p. 348-58.
767. Ringe, J.D. and J.J. Body, *A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover.* Clin Exp Rheumatol, 2007. **25**(5): p. 766-74.
768. Duncan, A.R., *The use of subcutaneous pamidronate.* J Pain Symptom Manage, 2003. **26**(1): p. 592-3.
769. Ward, L., et al., *Bisphosphonate therapy for children and adolescents with secondary osteoporosis.* Cochrane Database Syst Rev, 2007(4): p. CD005324.
770. Scottish Dental Clinical Effectiveness Programme. *Oral Health Management of Patients Prescribed Bisphosphonates: Dental Clinical Guidance*. 2011; April [Available from: www.sdcep.org.uk.
771. Phillipi, C.A., T. Remmington, and R.D. Steiner, *Bisphosphonate therapy for osteogenesis imperfecta.* Cochrane Database Syst Rev, 2008(4): p. CD005088.
772. Leblicq, C., et al., *Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia.* Pediatr Blood Cancer, 2013. **60**(5): p. 741-7.

773. Pillai Riddell, R.R., et al., *Non-pharmacological management of infant and young child procedural pain.* Cochrane Database Syst Rev, 2011(10): p. CD006275.
774. Uman, L.S., et al., *Psychological interventions for needle-related procedural pain and distress in children and adolescents.* Cochrane Database Syst Rev, 2006(4): p. CD005179.
775. Wong, I., C. St John-Green, and S.M. Walker, *Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children.* Paediatr Anaesth, 2013. **23**(6): p. 475-95.
776. Wong, T., et al., *Combined and alternating paracetamol and ibuprofen therapy for febrile children.* Cochrane Database Syst Rev, 2013. **10**: p. CD009572.
777. Rowland, A.G., et al., *Review of the efficacy of rectal paraldehyde in the management of acute and prolonged tonic-clonic convulsions.* Arch Dis Child, 2009. **94**(9): p. 720-3.
778. Ahmad, S., et al., *Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial.* Lancet, 2006. **367**(9522): p. 1591-7.
779. Armstrong, D.L. and M.R. Battin, *Pervasive seizures caused by hypoxic-ischemic encephalopathy: treatment with intravenous paraldehyde.* J Child Neurol, 2001. **16**(12): p. 915-7.
780. Giacoia, G.P., et al., *Pharmacokinetics of paraldehyde disposition in the neonate.* J Pediatr, 1984. **104**(2): p. 291-6.
781. Koren, G., et al., *Intravenous paraldehyde for seizure control in newborn infants.* Neurology, 1986. **36**(1): p. 108-11.
782. Appleton, R., S. Macleod, and T. Martland, *Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children.* Cochrane Database Syst Rev, 2008(3): p. CD001905.
783. Yoong, M., R.F. Chin, and R.C. Scott, *Management of convulsive status epilepticus in children.* Arch Dis Child Educ Pract Ed, 2009. **94**(1): p. 1-9.
784. Osorio, I., R.C. Reed, and J.N. Peltzer, *Refractory idiopathic absence status epilepticus: A probable paradoxical effect of phenytoin and carbamazepine.* Epilepsia, 2000. **41**(7): p. 887-94.
785. Bourgeois, B.F. and W.E. Dodson, *Phenytoin elimination in newborns.* Neurology, 1983. **33**(2): p. 173-8.
786. Tudur Smith, C., A.G. Marson, and P.R. Williamson, *Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures.* Cochrane Database Syst Rev, 2001(4): p. CD001769.
787. Tudur Smith, C., et al., *Carbamazepine versus phenytoin monotherapy for epilepsy.* Cochrane Database Syst Rev, 2002(2): p. CD001911.
788. McCleane, G.J., *Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study.* Anesth Analg, 1999. **89**(4): p. 985-8.
789. Mendoza, J., et al., *Systematic review: the adverse effects of sodium phosphate enema.* Aliment Pharmacol Ther, 2007. **26**(1): p. 9-20.
790. Miles C, F.D., Goodman ML, Wilkinson SSM. , *Laxatives for the management of constipation in palliative care patients.* The Cochrane Collaboration.; The Cochrane Library. 2009: JohnWiley&Sons, Ltd.
791. Biebl, A., A. Grillenberger, and K. Schmitt, *Enema-induced severe hyperphosphatemia in children.* Eur J Pediatr, 2009. **168**(1): p. 111-2.
792. NICE, *Constipation in children and young people: diagnosis and management.* , 2010.

793. Munez-Sanchez MJ, Leughton Swaneck S, and D. F., *Tetany secondary to phosphate enema toxicity, case report. .* Rev Child Pediatr 2017. **88**(3): p. 383-387.
794. Kalita, J., et al., *An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache.* J Neurol Sci, 2014. **342**(1-2): p. 127-32.
795. Felicia, B., *Pregabalin: a new approach to treatment of the dysautonomic crisis. .* Pediatrics, 2009. **124**(2): p. 743-746.
796. Saltik, S., et al., *Pregabalin Treatment of a Patient With Complex Regional Pain Syndrome.* Pediatr Neurol, 2016. **54**: p. 88-90.
797. NICE, *Neuropathic Pain in adults: pharmacological management in non-specialist settings.*, reviewed Feb 2017.
798. Dickman A and Schneider J, *The Syringe Driver. Continuous Infusions in Palliative Care*. 3rd ed. 2011: Oxford University Press.
799. Bell, S.G., *Gastroesophageal reflux and histamine2 antagonists.* Neonatal Netw, 2003. **22**(2): p. 53-7.
800. Tighe, M.P., et al., *Current pharmacological management of gastro-esophageal reflux in children: an evidence-based systematic review.* Paediatr Drugs, 2009. **11**(3): p. 185-202.
801. Moayyedi, P., et al., *Pharmacological interventions for non-ulcer dyspepsia.* Cochrane Database Syst Rev, 2006(4): p. CD001960.
802. Wang, Y., et al., *Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough.* Cochrane Database Syst Rev, 2009(4): p. CD004275.
803. Grassi, E., et al., *Risperidone in idiopathic and symptomatic dystonia: preliminary experience.* Neurol Sci, 2000. **21**(2): p. 121-3.
804. Kenrick S, f.S., *Treatment guidelines for symptom crises in Juvenile Battens Disease*, 2011.
805. Okamoto, Y., et al., *A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients.* J Pain Symptom Manage, 2007. **34**(2): p. 217-22.
806. Turkel, S.B., J.R. Jacobson, and C.J. Tavare, *The diagnosis and management of delirium in infancy.* J Child Adolesc Psychopharmacol, 2013. **23**(5): p. 352-6.
807. Brahmbhatt, K. and E. Whitgob, *Diagnosis and Management of Delirium in Critically Ill Infants: Case Report and Review.* Pediatrics, 2016. **137**(3): p. e20151940.
808. Schieveld, J.N., et al., *Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit.* Intensive Care Med, 2007. **33**(6): p. 1033-40.
809. BTS/SIGN. *British Guideline on the management of asthma. National clinical guideline*. 2014; May 2008 revised Jan 2014 [Available from: www.sign.ac.uk/guidelines/fulltext/141.
810. Chavasse, R., et al., *Short acting beta agonists for recurrent wheeze in children under 2 years of age.* Cochrane Database Syst Rev, 2002(3): p. CD002873.
811. Khirani, S., et al., *Effect of Salbutamol on Respiratory Muscle Strength in Spinal Muscular Atrophy.* Pediatr Neurol, 2017. **73**: p. 78-87 e1.
812. Pane, M., et al., *Daily salbutamol in young patients with SMA type II.* Neuromuscul Disord, 2008. **18**(7): p. 536-40.
813. Frongia, A.L., et al., *Salbutamol tolerability and efficacy in patients with spinal muscular atrophy type II.* Neuromuscul Disord, 2019. **29**(7): p. 517-524.
814. Burke, G., et al., *Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations.* Neuromuscul Disord, 2013. **23**(2): p. 170-5.
815. Candy, B., et al., *Laxatives for the management of constipation in people receiving palliative care.* Cochrane Database Syst Rev, 2015(5): p. CD003448.

816. Larkin, P.J., et al., *The management of constipation in palliative care: clinical practice recommendations.* Palliat Med, 2008. **22**(7): p. 796-807.
817. Sykes N, *Constipation and diarrhoea*, in *Oxford textbook of palliative medicine*, Cherny NI, Fallon MT, and et al. (Eds), Editors. 2015, Oxford University Press. p. 675-685.
818. Twycross, R., et al., *Stimulant laxatives and opioid-induced constipation.* J Pain Symptom Manage, 2012. **43**(2): p. 306-13.
819. Kochhar, R., et al., *Rectal sucralfate in radiation proctitis.* Lancet, 1988. **2**(8607): p. 400.
820. NHS Scotland, *Scottish Palliative Care Guidelines – Bleeding* 2014.
821. Regnard C and Makin W, *Management of bleeding in advanced cancer: a flow diagram. .* Palliative Medicine, 1992. **6**: p. 74-8.
822. Stockley IH, *Stockleys Drug Interactions*. 6th ed. 2002, London: Pharmaceutical Press
823. McCullough, R.W., *Practice insights on patient care-management overview for chemoradiation toxic mucositis-guidelines, guideline-supported therapies and high potency polymerized cross-linked sucralfate (ProThelial).* J Oncol Pharm Pract, 2019. **25**(2): p. 409-422.
824. McElvanna, K., A. Wilson, and T. Irwin, *Sucralfate paste enema: a new method of topical treatment for haemorrhagic radiation proctitis.* Colorectal Dis, 2014. **16**(4): p. 281-4.
825. Harrison, D., et al., *Utilization of analgesics, sedatives, and pain scores in infants with a prolonged hospitalization: a prospective descriptive cohort study.* Int J Nurs Stud, 2009. **46**(5): p. 624-32.
826. Harrison, D., et al., *Efficacy of sweet solutions for analgesia in infants between 1 and 12 months of age: a systematic review.* Arch Dis Child, 2010. **95**(6): p. 406-13.
827. Shah, P.S., et al., *Breastfeeding or breast milk for procedural pain in neonates.* Cochrane Database Syst Rev, 2012. **12**: p. CD004950.
828. Stevens, B., et al., *Sucrose for analgesia in newborn infants undergoing painful procedures.* Cochrane Database Syst Rev, 2013(1): p. CD001069.
829. Stevens, B., et al., *The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial.* BMC Pediatr, 2018. **18**(1): p. 85.
830. Finkel, J.C., et al., *First evaluation of tapentadol oral solution for the treatment of moderate to severe acute pain in children aged 6 to <18.* J Pain Res, 2019. **12**: p. 1925-1936.
831. Muse, D., et al., *Pharmacokinetics, safety, and efficacy of tapentadol oral solution for treating moderate to severe pain in pediatric patients.* J Pain Res, 2019. **12**: p. 1777-1790.
832. Kress, H.G. and F. Coluzzi, *Tapentadol in the management of cancer pain: current evidence and future perspectives.* J Pain Res, 2019. **12**: p. 1553-1560.
833. Freo, U., P. Romualdi, and H.G. Kress, *Tapentadol for neuropathic pain: a review of clinical studies.* J Pain Res, 2019. **12**: p. 1537-1551.
834. Dickenson, A.H. and H.G. Kress, *Tapentadol: a new option for the treatment of cancer and noncancer pains.* J Pain Res, 2019. **12**: p. 1509-1511.
835. Wiffen, P.J., et al., *Oral tapentadol for cancer pain.* Cochrane Database Syst Rev, 2015(9): p. CD011460.
836. Henney, H.R., 3rd and M. Chez, *Pediatric safety of tizanidine: clinical adverse event database and retrospective chart assessment.* Paediatr Drugs, 2009. **11**(6): p. 397-406.
837. Palazon Garcia, R., A. Benavente Valdepenas, and O. Arroyo Riano, *[Protocol for tizanidine use in infantile cerebral palsy].* An Pediatr (Barc), 2008. **68**(5): p. 511-5.
838. Vasquez-Briceno, A., et al., *[The usefulness of tizanidine. A one-year follow-up of the treatment of spasticity in infantile cerebral palsy].* Rev Neurol, 2006. **43**(3): p. 132-6.

839. Dai, A.I., S.N. Aksoy, and A.T. Demiryurek, *Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children With Cerebral Palsy and Spastic Equinus Foot Deformity.* J Child Neurol, 2016. **31**(2): p. 184-9.
840. Chung, C.Y., C.L. Chen, and A.M. Wong, *Pharmacotherapy of spasticity in children with cerebral palsy.* J Formos Med Assoc, 2011. **110**(4): p. 215-22.
841. Quality Standards Subcommittee of the American Academy of, N., et al., *Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.* Neurology, 2010. **74**(4): p. 336-43.
842. Friedrichsdorf, S.J., et al., *Tramadol versus codeine/acetaminophen after pediatric tonsillectomy: A prospective, double-blinded, randomized controlled trial.* J Opioid Manag, 2015. **11**(4): p. 283-94.
843. Dancel, R., E.A. Liles, and D. Fiore, *Acute Pain Management in Hospitalized Children.* Rev Recent Clin Trials, 2017. **12**(4): p. 277-283.
844. Kluger, M., et al., *Accuracy of dispersing tramadol capsules for oral administration in young children.* Anaesth Intensive Care, 2016. **44**(6): p. 742-744.
845. Calligaris, L., P. Marzuillo, and E. Barbi, *Re: Tramadol can selectively manage moderate pain in children following European advice limiting codeine use.* Acta Paediatr, 2014. **103**(11): p. e466.
846. Chauhan, S., et al., *Tranexamic acid in paediatric cardiac surgery.* Indian J Med Res, 2003. **118**: p. 86-9.
847. Frachon, X., et al., *Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000-2002).* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005. **99**(3): p. 270-5.
848. Graff, G.R., *Treatment of recurrent severe hemoptysis in cystic fibrosis with tranexamic acid.* Respiration, 2001. **68**(1): p. 91-4.
849. Mehta, R. and A.D. Shapiro, *Plasminogen deficiency.* Haemophilia, 2008. **14**(6): p. 1261-8.
850. Morimoto, Y., et al., *Haemostatic management of intraoral bleeding in patients with von Willebrand disease.* Oral Dis, 2005. **11**(4): p. 243-8.
851. Pereira, J. and T. Phan, *Management of bleeding in patients with advanced cancer.* Oncologist, 2004. **9**(5): p. 561-70.
852. Fahn, S., *High dosage anticholinergic therapy in dystonia.* Neurology, 1983. **33**(10): p. 1255-61.
853. Ben-Pazi, H., *Trihexyphenidyl improves motor function in children with dystonic cerebral palsy: a retrospective analysis.* J Child Neurol, 2011. **26**(7): p. 810-6.
854. Rice, J. and M.C. Waugh, *Pilot study on trihexyphenidyl in the treatment of dystonia in children with cerebral palsy.* J Child Neurol, 2009. **24**(2): p. 176-82.
855. Hoon, A.H., Jr., et al., *Age-dependent effects of trihexyphenidyl in extrapyramidal cerebral palsy.* Pediatr Neurol, 2001. **25**(1): p. 55-8.
856. Tsao, C.Y., *Low-dose trihexyphenidyl in the treatment of dystonia.* Pediatr Neurol, 1988. **4**(6): p. 381.
857. Marsden, C.D., M.H. Marion, and N. Quinn, *The treatment of severe dystonia in children and adults.* J Neurol Neurosurg Psychiatry, 1984. **47**(11): p. 1166-73.
858. Sanger, T.D., et al., *Prospective open-label clinical trial of trihexyphenidyl in children with secondary dystonia due to cerebral palsy.* J Child Neurol, 2007. **22**(5): p. 530-7.

859. Masson, R., E. Pagliano, and G. Baranello, *Efficacy of oral pharmacological treatments in dyskinetic cerebral palsy: a systematic review.* Dev Med Child Neurol, 2017. **59**(12): p. 1237-1248.
860. Jankovic, J., *Medical treatment of dystonia.* Mov Disord, 2013. **28**(7): p. 1001-12.
861. Brook L, V.J., Osborne C. , *Paediatric palliative care drug boxes; facilitating safe & effective symptom management at home at end of life.* Archives of Disease in Childhood, 2007. **92 (Suppl I): A58**.
862. Healthcare Improvement Scotland, *Scottish Adult Palliative Care Guidelines.*, N. Scotland, Editor 2014.
863. palliativedrugs.com.Ltd, *Essential independent palliative drug information for palliative and hospice care.*, 2018.
864. Editorial, *Gabapentin to Pregabalin Switch for Neuropathic Pain*, in *The Australian Pain Society Newsletter*2013.
865. Scotland, N. *Scottish palliative care Guidelines – Neuropathic pain*. 2019; Available from: http://www.palliativecareguidelines.scot.nhs.uk/guidelines/pain/neuropathic-pain.aspx.
866. Tayside-Prescriber. *Management of Neuropathic Pain* 2010; 118:[Available from: http://www.nhstaysideadtc.scot.nhs.uk/approved/bulletin/taypres/2010/Tayside%20Prescriber%20Management%20of%20Neuropathic%20pain%20118%20November%202010.pdf