

# **The Association of Paediatric Palliative Medicine Master Formulary 3rd edition**

## **2015**



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## Foreword

The first edition and second editions of the Association for Paediatric Palliative Medicine Master Formulary published in January 2011 and June 2012, both generated considerable interest. The first edition was the first attempt to collate all available dosing information to support prescribing in paediatric palliative care in a single volume.

The publication of the second edition was important, as it emphasised that the APPM Master Formulary was a sustainable resource, but also one that needed to be updated at regular intervals as the evidence base developed.

The publication of the third edition follows as part of the evolution of the Master Formulary, taking into account the ongoing feedback that clinicians are providing to the authors, based on their own practice. As such, the Master Formulary is becoming the major reference source from which other formularies are derived, not least as its reference list is being frequently updated.

Further evidence of its usefulness was that the second edition of the Master Formulary was translated into a number of languages, including Russian which, in turn, opened up new possibilities in terms of reaching a whole new group of clinicians who previously had to rely on reading the Formulary in English. In the third edition there are specific updates on methadone and clonidine, as well as a clear reference to the MHRA (Medicines and Healthcare Products Regulatory Agency) Statements on the use of codeine, domperidone and metoclopramide.

The APPM website indicates that there were 150 - 180 free downloads of the Formulary per month in 2014, and with the development of an App, it is hoped that access to it will continue to become even easier.

As with the previous editions, massive thanks goes to Dr Sat Jassal and Anita Aindow for their tireless work, as well as to a growing team who collectively have presented this update for your use. The development of a third edition in 2014 is another real achievement, and, as such, the Association of Paediatric Palliative Medicine is delighted to support this update, as well as regular revisions in the years to follow.

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## Introduction

Welcome to the third edition of the APPM formulary. Even in the short time between the publications of the two editions there have been some major changes in the use of certain medications. Many of the drugs have been extensively rewritten and references have been brought up to date. The publication of the WHO guide on pain 2012 is closely reflected in this document with the changes in the WHO ladder for pain.

We have decided that rather than produce lengthy monographs of each drug we would instead focus on key practice points pertaining to individual drugs. We have focused on use in palliative care and only included this specific use and excluded the better known and more general indications the view being that other information would be easily obtainable from other national formularies. We have included a note about the licensing status for each drug.

For each individual drug, evidence is cited from research papers (where available) on its usage. We have also cited the source(s) used for where drug dosages have been obtained. In many cases the evidence for use of some drugs has been either weak or extrapolated from adult dosages. In some situations dosage is based on clinical consensus. Although this is not necessarily the best way to give drugs to children we have been mindful of the fact that research of drug usage in children and specifically in children's palliative care is difficult, and as yet still in its infancy in this small but rapidly developing field.

We have included only those drugs, routes and indications generally used in children's palliative care in Great Britain. The drugs are presented here in alphabetical order by generic name. We would strongly advise practitioners not to prescribe outside their expertise, and if in doubt to consult the growing network of clinicians with specialist expertise in paediatric palliative medicine. For some drugs, higher doses than noted here may be recommended by specialists in the field familiar with their use.

We hope that over the course of time our colleagues around the world will communicate to us ways in which we can improve this formulary. Please do let us know of any omissions or additions that you feel we should add to the formulary by e-mailing [appm@togetherforshortlives.org.uk](mailto:appm@togetherforshortlives.org.uk).

It is hoped that other formularies in books or hospitals will base their information on this master formulary in the field of paediatric palliative medicine. All the key paediatric palliative formularies used around the UK have already agreed to adopt the style and content of this master formulary.

This formulary is provided free of charge and all the contributors work to improve paediatric palliative care around the world. Feel free to make as many copies as you like but please do not alter, plagiarise or try to copy any of the work into your own name. If you wish to use the work in a specific way then contact us for approval ([sat.jassal@gmail.com](mailto:sat.jassal@gmail.com)).

## Abbreviations

RE = strong research evidence

SR = some weak research evidence

CC = no published evidence but has clinical consensus

EA = evidence (research or clinical consensus) with adults

SC = subcutaneous

IV = intravenous

IM= intramuscular

CSCI = continuous subcutaneous infusion

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)[1], British National Formulary for Children (BNFC) [2], Neonatal Formulary[3], WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses[4], Palliative Care Formulary[5] and Medicines for Children[6]. 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 2014, 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.*

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## **Formulary**

### **Adrenaline** (topical)

Use:

Small external bleeds.

Dose and routes:

Soak gauze in 1:1000 (1 mg/mL) solution and apply directly to bleeding point.

Evidence: [1] CC

### **Alfentanil**

Use:

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

Dose and Routes:

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

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

- **Neonate:** 5-20 micrograms/kg initial dose, supplemental doses up to 10 micrograms/kg,
- **1 month to 18 years:** 10-20 micrograms/kg initial dose, up to 10 micrograms/kg supplemental doses.

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

- **Neonate:** 10-50 micrograms/kg over 10 minutes then 30-60 micrograms /kg/ hour,
- **1 month to 18 years:** 50-100 microgram/kg loading dose over 10 minutes, then 30-60microgram/kg/hour as a continuous infusion

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

Doses should be based on opioid equivalence with the following suggested as safe and practical conversion ratios

Oral morphine to CSCI alfentanil: 1/30<sup>th</sup> of the 24 hour total oral morphine dose e.g.  
60mg/24hours oral morphine = 2mg/24 hours CSCI alfentanil

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



CSCI diamorphine to CSCI alfentanil:  $1/10^{\text{th}}$  of the 24 hour total diamorphine dose e.g.  
 $30\text{mg}/24 \text{ hours diamorphine} = 3\text{mg}/24 \text{ hours CSCI alfentanil}$

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

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

### ***Breakthrough pain SEEK SPECIALIST ADVICE***

SC / Sublingual / Buccal

Suggest  $1/6^{\text{th}}$  to  $1/10^{\text{th}}$  of the total CSCI dose. However there is a poor relationship between the effective PRN dose and the regular background dose. Alfentanil has a short duration of action (~30 minutes) and even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Dose and frequency of administration should be regularly reviewed.

### ***Procedure-related pain SEEK SPECIALIST ADVICE***

SC / Sublingual / Buccal

- **Adults:** 250-500microgram single dose
- **Child:** 5microgram/kg single dose

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

#### Notes:

- Alfentanil injection is licensed for use in children as an analgesic supplement for use before and during anaesthesia. Use for pain relief in palliative care is unlicensed. Buccal, sublingual or intranasal administration of alfentanil for incident/breakthrough pain is an unlicensed indication and route of administration. The injection solution may be used for buccal, sublingual or intranasal administration (unlicensed).
- There is limited information / evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.
- Potency: 10-20 times stronger than parenteral morphine, approximately 25% of the potency of fentanyl.
- Very useful in patients with severe renal failure (no dose reduction is needed). May need to reduce the dose in severe hepatic impairment.
- In order to avoid excessive dosage in obese children, the dose may need to be calculated on the basis of ideal weight for height, rather than actual weight.
- Pharmacokinetics: half-life is prolonged in neonates, so can accumulate in prolonged use. Clearance may be increased from 1 month to 12 years of age, so higher infusion doses may be needed.
- Contraindication: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Interaction: alfentanil levels are increased by inhibitors of Cytochrome P450.

- Adverse effects include respiratory depression, hypotension, hypothermia, muscle rigidity (which can be managed with neuromuscular blocking drugs).
- For SC or IV infusion, alfentanil is compatible with 0.9% NaCl or 5% glucose as a diluent. For CSCI alfentanil appears compatible with most drugs used in a syringe driver. Like diamorphine, high doses of alfentanil may be dissolved in small volumes of diluent which is very useful for SC administration.
- Available as: injection (500 microgram/mL in 2ml and 10ml 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: each 'spray' delivers 0.14ml = 140 microgram alfentanil).

Evidence: [1, 5-9]

EA, RE (for PICU settings), CC (in palliative care settings outside ICU)

## Amitriptyline

Use:

- Neuropathic pain.

Dose and routes:

By mouth:

- **Child 2–12 years:** initial dose of 200microgram/kg (maximum 10 mg) given once daily at night. Dose may be increased gradually, if necessary, to a suggested maximum of 1mg/kg/dose twice daily (under specialist supervision).
- **Child 12–18 years:** initial dose of 10 mg at night increased gradually, if necessary, every 3-5 days to a suggested initial maximum of 75 mg/day. Higher doses up to 150 mg/day in divided doses may be used under specialist advice.

Notes:

- Not licensed for use in children with neuropathic pain.
- Analgesic effect unlikely to be evident for several days. Potential improved sleep and appetite which are likely to precede analgesic effect.
- Drug interactions: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation. Caution with concurrent use of drugs which inhibit or induce CYP2D6 enzymes.
- Main side effects limiting use in children include; constipation, dry mouth and drowsiness.
- Liquid may be administered via an enteral feeding tube.
- Available as: tablets (10 mg, 25 mg, 50 mg) and oral solution (25 mg/5 mL, 50mg/5mL).

Evidence: [1, 10-12]

## Aprepitant

### Use:

- Prevention and treatment of nausea and vomiting associated with emetogenic cancer chemotherapy

### Dose and route:

#### For oral administration:

- **Child** <10 years: 3mg/kg (max 125mg) as a single dose on Day 1 (1 hour before chemotherapy) followed by 2mg/kg (max 80mg) as a single dose on Day 2 and Day 3
- **Child** >10 years: 125mg as a single dose on Day 1 (1 hour before chemotherapy) followed by 80mg as a single dose on Day 2 and Day 3

Aprepitant is used in combination with a corticosteroid (usually dexamethasone) and a 5-HT<sub>3</sub> 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
- Aprepitant is not licensed for use in children and adolescents less than 18 years of age (although a number of clinical trials are currently ongoing). Limited evidence for use in those less than 10 years of age
- Aprepitant is a selective high-affinity antagonist at NK<sub>1</sub> receptors
- Aprepitant is a substrate, a moderate inhibitor and inducer of the CYP3A4 isoenzyme system. It is also an inducer of CYP2C9 and therefore has the potential to interact with any other drugs that are also metabolised by these enzyme systems including rifampicin, carbamazepine, phenobarbital, itraconazole, clarithromycin, warfarin and dexamethasone. Please note this list is not exhaustive – seek advice.
- Common side effects include hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache and dizziness
- Available as: capsules 80mg and 125mg. A formulation for extemporaneous preparation of an oral suspension is available.

Evidence: [1, 5, 13-17]

## Arachis Oil Enema

### Use:

- Faecal softener
- Faecal impaction

### Dose and route:

#### By rectal administration

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

### Notes:

- Caution: as arachis oil is derived from peanuts, do not use in children with a known allergy to peanuts.
- Generally used as a retention enema to soften impacted faeces. May be instilled and left overnight to soften the stool.
- Warm enema before use by placing in warm water.
- Administration may cause local irritation.
- Licensed for use in children from 3 years of age.
- Available as: enema, arachis (peanut) oil in 130 mL single dose disposable packs.

Evidence: [1, 6] CC

## Aspirin

### Use:

- Mild to moderate pain.
- Pyrexia.

### Dose and routes:

#### By mouth:

- **> 16 years of age:** Initial dose of 300 mg every 4–6 hours when necessary. Dose may be increased if necessary to a maximum of 900 mg every 4-6 hours (maximum 4 g/day).

### Notes:

- Contraindicated in children due to risk of Reye Syndrome.
- Use with caution in asthma, previous peptic ulceration, severe hepatic or renal impairment.
- May be used in low dose under specialist advice for children with some cardiac conditions.
- Available as: tablets (75 mg, 300 mg), dispersible tablets (75 mg, 300 mg), and suppositories (150 mg available from special-order manufacturers or specialist importing companies).

Evidence: [1]

## Baclofen

### Use:

- Chronic severe spasticity of voluntary muscle
- Considered as third line neuropathic agent

### Dose and routes:

#### By mouth:

- **Initial dose for child under 18 years:** 300microgram/kg/day in 4 divided doses (maximum single dose 2.5 mg) increased gradually at weekly intervals to a usual maintenance dose of 0.75-2 mg/kg/day in divided doses with the following maximum daily doses:
- **Child up to 8 years:** maximum total daily dose 40 mg/day,
- **Child 8-18 years:** maximum total daily dose 60 mg/day,

### Notes:

- Review treatment if no benefit within 6 weeks of achieving maximum dose.
- There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.
- Monitor and review reduction in muscle tone and potential adverse effects on swallow and airway protection.
- Avoid abrupt withdrawal.
- Intrathecal use by specialist only.
- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.
- Contraindicated if there is a history of active peptic ulceration.
- Administration with or after food may minimise gastric irritation.
- May be administered via enteral feeding tubes. Use liquid formulation for small doses, dilute prior to use to reduce viscosity. Consider dispersing tablets in water for higher doses owing to the sorbitol content of the liquid formulation.
- Available as: tablets (10 mg) and oral solution (5 mg/5 mL).

Evidence: [1, 2, 12, 18-25]

## Bethanechol

### Use:

- Opioid induced urinary retention

### Dose and routes:

#### By mouth:

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

#### Subcutaneous:

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

#### Notes

- The safety and efficacy of bethanechol in children has not been established (bethanechol is not licensed for use in children).
- Preferably taken before food to reduce potential for nausea and vomiting.
- Contraindicated in hyperthyroidism, peptic ulcer, asthma, cardiac disease and epilepsy.
- Tablets may be crushed and dispersed in water for administration via an enteral feeding tube; formulation for extemporaneous oral suspension is available.
- Available as: tablets (10 mg and 25 mg), injection for subcutaneous injection only (5 mg/mL – not licensed in the UK but may be possible to import via a specialist importation company).

Evidence: [12, 26, 27]

## Bisacodyl

#### Use:

- Constipation

#### Dose and routes:

##### By mouth:

- **Child 4–18 years:** 5-20mg once daily; adjust according to response.

##### By rectum (suppository):

- **Child 2–18 years:** 5-10 mg once daily; adjust according to response.

#### Notes:

- Tablets act in 10–12 hours. Suppositories act in 20–60 min; suppositories must be in direct contact with mucosal wall.
- Stimulant laxative.
- Prolonged or excessive use can cause electrolyte disturbance.
- Available as: tablets (5 mg) and suppositories (5 mg, 10 mg).

Evidence: [1, 2]

## Buprenorphine

### Use:

- Moderate to severe pain

### Dose and routes:

By sublingual route (starting doses):

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

By transdermal patch:

- By titration or as indicated by existing opioid needs.

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

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

### Notes:

- Sublingual tablets not licensed for use in children < 6 years old.
- Patches not licensed for use in children.
- Has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Sublingual duration of action 6-8 hours.
- Caution with hepatic impairment and potential interaction with many drugs including anti-retrovirals.
- Available as: tablets (200 microgram, 400 microgram) for sublingual administration. Tablets may be halved.
- Available as: two types of patches:
  1. *BuTrans*®—applied every 7 days. Available as 5 (5 microgram /hour for 7 days), 10 (10 microgram /hour for 7 days), and 20 (20 microgram /hour for 7 days)
  2. *TransTec*®—applied every 96 hours. Available as 35 (35 microgram /hour for 96 hours), 52.5 (52.5 microgram /hour for 96 hours), and 70 (70 microgram /hour for 96 hours).

For patches, systemic analgesic concentrations are generally reached within 12–24 hours but levels continue to rise for 32–54 hours. If converting from:

- 4-hourly oral morphine - give regular doses for the first 12 hours after applying the patch
- 12-hourly slow release morphine - apply the patch and give the final slow release dose at the same time
- 24-hourly slow release morphine - apply the patch 12 hours after the final slow release dose
- Continuous subcutaneous infusion - continue the syringe driver for about 12 hours after applying the patch.

- Effects only partially reversed by naloxone.
- Rate of absorption from patch is affected by temperature, so caution with pyrexia or increased external temperature such as hot baths: possibility of accidental overdose with respiratory depression.
- Patches are finding a use as an easily administered option for low dose background opioid analgesia in a stable situation, for example in severe neurological impairment.
- Schedule 3 CD

Evidence: [2, 5, 28-30]



## Carbamazepine

### Use:

- Neuropathic pain.
- Some movement disorders.
- Anticonvulsant

### Dose and routes

#### By mouth:

- **Child 1 month–12 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 12–18 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–18 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 leucopenia.
- Numerous interactions with other drugs including chemotherapy drugs.
- Different preparations may vary in bioavailability so avoid changing formulations or brands.
- Suppositories of 125 mg are approximately equivalent to 100 mg tablets.
- Oral liquid has been administered rectally – should be retained for at least 2 hours if possible but may have a laxative effect
- For administration via an enteral feeding tube use the liquid preparation. Dilute with an equal volume of water immediately prior to administration. If giving doses higher than 400 mg/day, divide into 4 equal doses.
- Available as: tablets (100 mg, 200 mg, 400 mg), chew tabs (100 mg, 200 mg), liquid (100 mg/5mL), suppositories (125 mg, 250 mg), and modified release tablets (200mg, 400 mg).

Evidence: [2, 12, 31-34]

## 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: 50 mg twice daily or 100mg daily
  - Weight more than 25 kg: 100 mg twice daily

### Notes

- Celecoxib is a cyclooxygenase-2 selective inhibitor
- Not licensed in the UK for use in children
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term. COX-2 inhibitors are associated with an increased risk of thrombotic effects.
- All NSAIDs are associated with serious gastro-intestinal toxicity. COX-2 inhibitors are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.
- Use with caution in patients with renal impairment and avoid in severe renal impairment.
- Use with caution in hepatic impairment.
- Celecoxib interacts with a great many commonly used drugs, check BNF (current version on-line).
- Capsules may be opened and contents mixed with soft food immediately before administration. For a 50mg dose, approximately halve the 100mg capsule contents to give a best estimate of a 50mg dose.
- Available as: capsules 100mg, 200mg.

Evidence: [1, 35-38] SR

## Chloral hydrate

### Use:

- Insomnia.
- Agitation

### Dose and routes:

#### By mouth or rectum:

- **Neonate:** initial dose of 30 mg/kg as a single dose at night. May be increased to 45 mg/kg at night or when required,
- **Child 1 month–12 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 12–18 years:** initial dose of 500 mg as a single dose at night or when required. Dose may be increased if necessary to 1-2 g. Maximum single dose 2 g.

### Notes:

- Not licensed in agitation or in infants <2 years for insomnia
- Oral use: mix with plenty of juice, water, or milk to reduce gastric irritation and disguise the unpleasant taste.
- For rectal administration use oral solution or suppositories (available from 'specials' manufacturers).
- Accumulates on prolonged use and should be avoided in severe renal or hepatic impairment.
- Available as: tablets (chloral betaine 707 mg = chloral 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 25mg, 50 mg, 60 mg, 100 mg, 200 mg, 500 mg from 'specials' manufacturers).

Evidence: [2, 3, 6, 39-41]

## Chlorpromazine

### Use:

- Hiccups
- Nausea and vomiting of terminal illness (where other drugs are unsuitable)

### Dose and routes:

#### *Hiccups*

##### By mouth:

- **Child 1–6 years:** 500 micrograms/kg every 4–6 hours adjusted according to response (maximum 40 mg daily),
- **Child 6–12 years:** 10 mg 3 times daily, adjusted according to response (maximum 75 mg daily),
- **Child 12–18 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 1–6 years:** 500 micrograms/kg every 4–6 hours; maximum 40 mg daily,
- **Child 6–12 years:** 500 micrograms/kg every 4–6 hours; maximum 75 mg daily,
- **Child 12–18 years:** 10–25 mg every 4–6 hours.

##### By deep intramuscular injection:

- **Child 1–6 years:** 500 micrograms/kg every 6–8 hours; maximum 40 mg daily,
- **Child 6–12 years:** 500 micrograms/kg every 6–8 hours; maximum 75 mg daily,
- **Child 12–18 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.
- Available as: tablets, coated (25 mg, 50 mg, 100 mg); oral solution (25 mg/5 mL, 100 mg/ 5mL); injection (25 mg/mL in 1mL and 2mL ampoules).

Evidence: [1, 2, 42-50]

## Clobazam

### Uses:

- Adjunctive therapy for epilepsy

### Dose and route:

#### For oral administration:

- **Child 1 month - 6 years:** initial dose of 125 microgram/kg twice daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 250 microgram/kg twice daily. Maximum dose 500 microgram/kg (15 mg single dose) twice daily,
- **Child 6-18 years:** initial dose of 5 mg daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 0.3-1 mg/kg daily. Maximum 60 mg daily. Daily doses of up to 30 mg may be given as a single dose at bedtime, higher doses should be divided.

### Notes:

- Not licensed for use in children less than 6 years of age.
- Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations.
- Tablets can be administered whole, or crushed and mixed in apple sauce. The 10mg tablets can be divided into equal halves of 5mg. Clobazam can be given with or without food.
- Possible side-effects as would be expected from benzodiazepines. Children are more susceptible to sedation and paradoxical emotional reactions.
- Available as: tablets (10mg Frisium<sup>(R)</sup>); tablets (5mg – unlicensed and available on a named-patient basis); oral liquid (5mg in 5ml and 10mg in 5ml – care with differing strengths).
- Frisium<sup>(R)</sup> tablets are NHS black-listed except for epilepsy and endorsed 'SLS'.

Evidence: [2, 6]

## Clonazepam

### Use:

- Tonic-clonic seizures
- Partial seizures
- Cluster seizures
- Myoclonus
- Status epilepticus (3<sup>rd</sup> line, particularly in neonates)
- Neuropathic pain
- Restless legs
- Gasping
- Anxiety and panic

### Dose and routes:

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

- **Child 1 month–1 year:** initially 250micrograms 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 1–5 years:** initially 250micrograms 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 5–12 years:** initially 500micrograms 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 12–18 years:** initially 1 mg at night for 4 nights, increased over 2–4 weeks to usual maintenance of 4–8 mg at night (may be given in 3 divided doses if necessary).

*For status epilepticus: (SR)*

### Continuous subcutaneous Infusion:

- **Child 1 month – 18 years:** starting dose 20 - 25 microgram/kg/24 hours,
- Maximum starting doses: 1-5 years: 250 microgram/24 hours;  
5-12 years: 500 microgram/24 hours
- Increase at intervals of not less than 12 hours to 200 microgram/kg/24 hours (maximum 8 mg/24 hours);
- Doses of up to 1.4 mg/kg/24 hours have been used in status epilepticus in PICU environment.

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

- **Neonate:** 100 microgram / kg intravenous over at least 2 minutes, repeated after 24 hours if necessary (avoid unless no safer alternative). Used for seizures not controlled with phenobarbital or phenytoin,
- **Child 1 month to 12 years:** loading dose 50 micrograms/kg (maximum 1 mg) by IV injection followed by IV infusion of 10 microgram/kg/hour adjusted according to response; maximum 60 micrograms/kg/hour,
- **Child 12-18 years:** loading dose 1 mg by IV injection followed by IV infusion of 10 microgram/kg/hour adjusted according to response; maximum 60 micrograms/kg/hour.

#### Notes

- Licensed for use in children for status epilepticus and epilepsy. Not licensed for neuropathic pain. Tablets licensed in children.
- Very effective anticonvulsant, usually 3<sup>rd</sup> line due to side effects and development of tolerance.
- Use lower doses for panic, anxiety, terminal sedation, neuropathic pain, and restless legs.
- Do not use in acute or severe respiratory insufficiency unless in the imminently dying. Be cautious in those with chronic respiratory disease
- As an anxiolytic / sedative clonazepam is approximately 20 times as potent as diazepam (i.e. 250 microgram clonazepam equivalent to 5 mg diazepam orally).
- Multiple indications in addition to anticonvulsant activity can make clonazepam particularly useful in the palliative care of children for neurological disorders.
- Many children with complex seizure disorders are on twice daily doses and on higher dosages.
- The dose may be increased for short periods 3-5 days with increased seizures e.g. from viral illness
- Elimination half life of 20 - 40 hours means that it may take up to 6 days to reach steady state; there is a risk of accumulation and toxicity with rapid increase of infusion; consider loading dose to reach steady state more quickly.
- Avoid abrupt withdrawal
- Associated with salivary hypersecretion and drooling
- Tablets may be dispersed in water for administration via an enteral feeding tube.
- Stability of diluted clonazepam is up to 12 hours so prescribers should consider 12 hourly infusions.
- Compatible with most drugs commonly administered via continuous subcutaneous infusion via syringe driver.
- Available as: tablets (500 microgram scored, 2 mg scored); liquid (0.5 mg in 5 mL and 2 mg in 5 mL now available as licensed preparations from Rosemont but not indicated in children due to high alcohol content; other unlicensed oral liquids are available from specials manufacturers); injection (1 mg/mL unlicensed).

Evidence: [2, 3, 24, 33, 51, 52]

## Clonidine

### Uses:

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

### Doses and routes:

#### *Anxiety / Sedation / Pre-procedure:*

##### *Oral / Intranasal / Rectal:*

- **Child >1 month:** 4 microgram/kg as a single dose (suggested maximum 150 microgram single dose). If used as premedicant prior to a procedure give 45-60 minutes before.

#### *Pain / Sedation / Opioid sparing / Prevention of opioid withdrawal effects (most experience on PICU):*

##### *Oral / IV Bolus:*

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

##### *IV infusion:*

- **Child >1 month:** 0.1-2 microgram/kg/hour.  
Usual starting doses:
  - **Child <6 months:** 0.4 microgram/kg/hour;
  - **Child >6 months:** 0.6 microgram/kg/hour

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

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

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

#### *Spasticity / Movement Disorder:*

##### *Oral:*

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

#### *Behavioural problems / Tics / Tourette's syndrome:*

##### *Oral:*

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



## Notes

- Clonidine is a mixed alpha-1 and alpha-2 agonist (mainly alpha-2). Appears to have synergistic analgesic effects with opioids and prevent opioid withdrawal symptoms. Also useful for its sedative effect. Use established in ADHD, behavioural problems and tics.
- Not licensed for use in children
- Licensed indication of clonidine is for the treatment of hypertension so reduction in BP is a likely side effect of use. Titrate the dose of clonidine against the symptoms and monitor BP and pulse on starting treatment and after each dose increase.
- When used for longer than a few days, clonidine should be withdrawn slowly on discontinuation to prevent acute withdrawal symptoms including rebound hypertension.
- Use with caution in those with bradyarrhythmia, Raynaud's or other occlusive peripheral vascular disease.
- Common side effects include constipation, nausea, dry mouth, vomiting, postural hypotension, dizziness, sleep disturbances, headache.
- Effects of clonidine are abolished by drugs with alpha-2 antagonistic activity e.g. tricyclics and antipsychotic drugs. Antihypertensive effects may be potentiated by other drugs used to lower BP.
- Oral bioavailability 75-100%; generally 1:1 conversion IV: oral is suggested as a starting point (largely adult data; note: it has been suggested that oral bioavailability may be lower in children [53]).
- Some reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4microgram/kg have been used.
- Onset of effect: oral 30-60 mins. Time to peak plasma concentration: oral 1.5-5 hours; epidural 20 minutes; transdermal 2 days.
- Clonidine has been used successfully by SC injection and infusion – seek specialist advice.
- Oral solution may be administered via an enteral feeding tube. Alternatively, if the required dose is appropriate to the available tablet strengths, the tablets may be crushed and dispersed in water for administration via an enteral feeding tube. Note: the 25microgram tablets do not appear to disperse in water as readily as the 100microgram tablets.
- Chronic conditions – for older children the use of transdermal patches may be considered when an effective oral dose has been established which is great enough to allow an approximate conversion (1:1) to the transdermal route. Although unlicensed in the UK, 3 strengths of patches are available programmed to release 100 microgram, 200 microgram or 300 microgram clonidine daily for 7 days.
- Available as: tablets 25 microgram, 100 microgram; injection 150 micrograms/ml; transdermal patch 100 microgram, 200 microgram or 300 microgram clonidine daily for 7 days (not licensed in UK – available via importation company); oral solution (special) 50 microgram/ml

Evidence: [53-67]

## Co-danthramer (dantron and poloxamer 188)

Use:

- Constipation in terminal illness only

Dose and routes:

By mouth:

Co-danthramer 25/200 suspension 5mL = one co-danthramer 25/200 capsule (Dantron 25 mg poloxamer '188' 200mg):

- **Child 2–12 years:** 2.5–5 mL at night,
- **Child 6–12 years:** 1 capsule at night,
- **Child 12–18 years:** 5–10 mL or 1–2 capsules at night. Dosage can be increased up to 10-20 mL twice a day.

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

- **Child 12–18 years:** 5 mL or 1–2 capsules at night.

Notes

- Co-danthramer is made from dantron and poloxamer '188'.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence/ children with nappies).
- Dantron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [1, 2]

## Co-danthrusate (Dantron and Docusate Sodium)

Use:

- Constipation in terminal illness only

Dose and routes:

By mouth:

Co-danthrusate 50/60 suspension 5 mL = one co-danthrusate 50/60 capsule (Dantron 50mg/ Docusate sodium 60mg)

- **Child 6–12 years:** 5 mL or 1 capsule at night,
- **Child 12–18 years:** 5–15 mL or 1–3 capsules at night.

Notes

- Co-danthrusate is made from dantron and docusate sodium.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence/ children with nappies).
- Danthron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [1, 2]

## Codeine Phosphate

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has addressed safety concerns with codeine-containing medicines when used for the management of pain in children June 2013. This follows the PRAC's review of reports of children who developed serious adverse effects or died after taking codeine for pain relief. Children who are 'ultra rapid metabolisers' of codeine are at risk of severe opioid toxicity due to rapid and uncontrolled conversion of codeine into morphine.

The PRAC recommended the following risk-minimisation measures to ensure that only children for whom benefits are greater than the risks are given the medicine for pain relief:

- Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other analgesics such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) with known obstructive airway disease or those who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/06/news\\_detail\\_001813.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001813.jsp&mid=WC0b01ac058004d5c1)

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

### Uses:

- Mild to moderate pain in patients who through previous use are known to be able to benefit when other agents are contraindicated or not appropriate. For when required use only – not suitable for management of background pain.
- Marked diarrhoea, when other agents are contra-indicated or not appropriate, with medication doses and interval titrated to effect
- Cough suppressant

### Dose and routes:

By mouth, rectum, SC injection, or by IM injection:

- **Neonate:** 0.5–1 mg/kg every 4–6 hours,
- **Child 1 month–12 years:** 0.5–1 mg/kg every 4–6 hours; maximum 240 mg daily,
- **Child 12–18 years:** 30–60 mg every 4–6 hours; maximum 240 mg daily.

*As cough suppressant in the form of pholcodine linctus/syrup (NB/ Different strengths are available)*

- **Child 6-12 years:** 2.5 mg 3-4 times daily,
- **Child 12-18 years:** 5-10 mg 3-4 times daily.

### Notes:

- Not licensed for use in children < 1 year old.
- Codeine is effectively a pro drug for morphine, delivering approximately 1 mg of morphine for every 10 mg of codeine.

- Pharmacologically, codeine is no different from morphine except that it is weaker and less consistently effective. This has led the WHO to recommend that it is better replaced by low doses of morphine.
- Conversion to morphine is subject to wide pharmacogenetic variation. 5-34% of population have an enzyme deficiency that prevents activation of codeine to active metabolite and so it is ineffective in this group.
- Individuals who are ultra-rapid metabolisers can develop life threatening opioid toxicity.
- Seems relatively constipating compared with morphine/ diamorphine, particularly in children.
- Rectal administration is an unlicensed route of administration using an unlicensed product.
- Must *not* be given IV.
- Reduce dose in renal impairment.
- Available as: tablets (15 mg, 30 mg, 60 mg), oral solution (25 mg/5 mL), injection (60 mg/mL), suppositories of various strengths available from 'specials' manufacturers. Pholcodine as linctus 2 mg/5 mL, 5 mg/5 mL and 10 mg/5 mL.
- Some retail pharmacies do not stock codeine phosphate solution at 25 mg/5 mL. They usually do stock codeine phosphate linctus at 15 mg/5 mL and this is worth enquiring of if a practitioner is working in the community and wishes to prescribe this medication. BE CAREFUL WITH DIFFERING STRENGTHS OF LIQUIDS.

Evidence: [1-3, 33, 68, 69]

## Cyclizine

### Use:

- Antiemetic of choice for raised intracranial pressure.
- Nausea and vomiting where other more specific antiemetics (metoclopramide, 5HT<sub>3</sub> antagonists) have failed

### Dose and routes:

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

- **Child 1 month–6 years:** 0.5–1 mg/kg up to 3 times daily; maximum single dose 25 mg,
- **Child 6–12 years:** 25 mg up to 3 times daily,
- **Child 12–18 years:** 50 mg up to 3 times daily.

By rectum:

- **Child 2–6 years:** 12.5 mg up to 3 times daily,
- **Child 6–12 years:** 25 mg up to 3 times daily,
- **Child 12–18 years:** 50 mg up to 3 times daily.

By continuous IV or SC infusion:

- **Child 1 month–5 years:** 3 mg/kg over 24 hours (maximum 50 mg/24 hours),
- **Child 6–12 years:** 75 mg over 24 hours,
- **Child 12–18 years:** 150 mg over 24 hours.

### Notes:

- Antihistaminic antimuscarinic antiemetic
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- Antimuscarinic side effects include dry mouth; drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Rapid SC or IV bolus can lead to 'lightheadness' –disliked by some and enthralling to others leading to repeated requests for IV Cyclizine.
- Care with subcutaneous or intravenous infusion – acidic pH and can cause injection site reactions
- For CSCI or IV infusion, dilute only with water for injection or 5% dextrose; *incompatible* with 0.9 % saline and will precipitate.
- Concentration dependant incompatibility with alfentanil, dexamethasone, diamorphine and oxycodone
- Suppositories must be kept refrigerated.
- Tablets may be crushed for oral administration. The tablets do not disperse well in water but if shaken in 10ml water for 5 minutes; the resulting dispersion may be administered immediately via an enteral feeding tube.
- Available as: tablets (50 mg), suppositories (12.5 mg, 25 mg, 50 mg, 100 mg from 'specials' manufacturers) and injection (50 mg/mL).

Evidence: [2, 12, 70]

## Dantrolene

### Use:

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

### Dose and routes:

The dose of dantrolene should be built up slowly

#### By mouth:

- **Child 5–12 years:** initial dose of 500 microgram/kg once daily; after 7 days increase to 500 microgram/kg/dose 3 times daily. Every 7 days increase by a further 500 microgram/kg/dose until response. Maximum recommended dose is 2 mg/kg 3–4 times daily (maximum total daily dose 400 mg),
- **Child 12–18 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 and diarrhoea
- Available as: capsules (25 mg, 100 mg), oral suspension (extemporaneous formulation).

Evidence: [2, 19, 20, 25, 71, 72]

## Dexamethasone

### Use

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

### Dose and routes

Prescribe as dexamethasone base

#### *Headache associated with raised intracranial pressure*

By mouth or IV:

**Child 1 month–12 years:** 250 microgram/kg twice a day for 5 days; then reduce or stop.

#### *To relieve symptoms of brain or other tumour*

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

#### *Antiemetic*

By mouth or IV:

- **Child < 1 year:** initial dose 250microgram 3 times daily. This dose may be increased as necessary and as tolerated up to 1 mg 3 times daily,
- **Child 1–5 years:** initial dose 1 mg 3 times daily. This dose may be increased as necessary and as tolerated up to 2 mg 3 times daily,
- **Child 6–12 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 12–18 years:** 4 mg 3 times daily.

### Notes:

- Not licensed for use in children as an antiemetic.
- Dexamethasone has high glucocorticoid activity but insignificant mineralocorticoid activity so is particularly suited for high dose anti-inflammatory therapy.
- Dexamethasone can be given in a single daily dose each morning for most indications; this reduces the likelihood of corticosteroid induced insomnia and agitation
- Dexamethasone has an oral bioavailability of >80%; it can be converted to SC or IV on a 1:1 basis
- Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg.
- Dexamethasone 1 mg = 7 mg prednisolone (anti-inflammatory equivalence).
- Dexamethasone has a long duration of action
- Problems of weight gain and Cushingoid appearance are major problems specifically in children. All specialist units therefore use pulsed dose regimes in preference to continual use. Regimes vary with conditions and specialist units. Seek local specialist advice.
- Other side effects include: diabetes, osteoporosis, muscle wasting, peptic ulceration and behavioural problems particularly agitation.
- Dexamethasone can be stopped abruptly if given for a short duration of time (<7days), otherwise gradual withdrawal is advised

- Tablets may be dispersed in water if oral liquid unavailable. Oral solution or tablets dispersed in water may be administered via an enteral feeding tube.
- Available as: tablets (500 microgram, 2 mg), oral solution (2 mg/5 mL and other strengths available from 'specials' manufacturers) and injection as dexamethasone sodium phosphate (equivalent to 4 mg/1 mL dexamethasone base (Organon<sup>R</sup> brand) or 3.3 mg/mL dexamethasone base (Hospira<sup>R</sup> brand).

Evidence: [6, 49, 73-76]



## Diamorphine

Use:

- Moderate to severe pain
- Dyspnoea

Dose and routes:

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

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

### *Acute or Chronic pain*

By continuous subcutaneous or intravenous infusion

- **Neonate:** Initial dose of 2.5 microgram/kg/hour which can be increased as necessary to a suggested maximum of 7 micrograms/kg/hour,
- **Child 1 month-18 years:** 7-25 microgram/kg/hour (initial maximum 10 mg/24 hours) adjusted according to response.

By IV /SC or IM injection:

- **Neonate:** 15 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 1-3 month:** 20 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 3-6 months:** 25-50 micrograms/kg every 6 hours as necessary, adjusted according to response,
- **Child 6-12 months:** 75 micrograms/kg every 4 hours as necessary, adjusted according to response,
- **Child 1-12 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5mg,
- **Child 12-18 years:** 75-100 micrograms/kg every 4 hours as necessary, adjusted according to response. Suggested initial maximum dose of 2.5-5mg.

By intranasal or buccal route:

- **Child over 10kg:** 50-100 micrograms/kg; maximum single dose 10 mg.  
Injection solution can be used by intranasal or buccal routes or Nasal spray (Ayendi<sup>(R)</sup>) now available and licensed for use in children aged 2 years and over (weight 12kg upwards) for the management of severe acute pain.

720microgram/actuation

- 12-18kg: 2 sprays as a single dose
- 18-24kg: 3 sprays as a single dose
- 24-30kg: 4 sprays as a single dose

1600microgram/actuation

- 30-40kg: 2 sprays as a single dose
- 40-50kg: 3 sprays as a single dose

### *Breakthrough*

By buccal, subcutaneous or IV routes

- For breakthrough pain use 5-10% of total daily diamorphine dose every 1-4 hours as needed.

*Dyspnoea*

By buccal, subcutaneous or IV routes

- Dose as for pain, but at 50% of breakthrough dose

Notes:

- Diamorphine injection is licensed for the treatment of children who are terminally ill.
- For intranasal or buccal administration of diamorphine use the injection powder reconstituted in water for injections (unlicensed route of administration) or the nasal spray may be used (licensed for use in the management of severe acute pain from 2 years of age)
- In neonates, dosage interval should be extended to 6 or 8 hourly depending on renal function and the dose carefully checked, due to increased sensitivity to opioids in the first year of life.
- In poor renal function, dosage interval may be lengthened, or opioids only given as required and titrated against symptoms. Consider changing to fentanyl.
- For CSCI dilute with water for injections, as concentration incompatibility occurs with 0.9% saline at above 40 mg/ ml.
- Diamorphine can be given by subcutaneous infusion up to a strength of 250mg/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.
- Available as : injection (5 mg, 10 mg, 30 mg, 100 mg, 500 mg ampoules); nasal spray 720microgram/actuation and 1600microgram/actuation (Ayendi Nasal Spray<sup>(R)</sup>).

Evidence: [1, 2, 6, 33, 77, 78]

## 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 2–12 years:** 1-2mg 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 1–12 months:** initial dose of 250 microgram/kg twice a day,
- **Child 1–5 years:** initial dose of 2.5 mg twice a day,
- **Child 5–12 years:** initial dose of 5 mg twice a day,
- **Child 12–18 years:** initial dose of 10 mg twice a day; maximum total daily dose 40 mg.

*Status epilepticus*

#### By IV injection over 3–5 minutes:

**Neonate:** 300-400 micrograms/kg as a single dose repeated once after 10 minutes if necessary

**Child 1 month – 12 years:** 300-400 micrograms per kg (max 10 mg) repeated once after 10 minutes if necessary

**Child 12–18 years:** 10 mg repeated once after 10 minutes if necessary (In hospital up to 20 mg as single dose may be used).

#### By rectum (rectal solution):

- **Neonate:** 1.25–2.5 mg repeated once after 10 minutes if necessary,
- **Child 1 month–2 years:** 5 mg repeated once after 10 minutes if necessary,
- **Child 2–12 years:** 5–10 mg repeated once after 10 minutes if necessary,
- **Child 12–18 years:** 10 mg repeated once after 10 minutes if necessary (in hospital up to 20 mg as a single dose may be used).

### Notes

- Do not use in acute or severe respiratory insufficiency unless in the imminently dying
- Rectal tubes not licensed for children < 1 year old.
- Use with caution in mild-moderate hepatic disease
- Metabolised via the cytochrome P450 group of liver enzymes – potential for interaction with any concurrent medicine that induces or inhibits this group of enzymes. Enhancement of the central depressive effect may occur if diazepam is combined with drugs such as neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates and sedative antihistamines
- Can cause dose-dependent drowsiness and impaired psychomotor and cognitive skills
- Almost 100% bioavailable when given orally or by rectal solution

- Onset of action ~15 minutes given orally and within 1-5 minutes given intravenously. Given as rectal solution, diazepam is rapidly absorbed from the rectal mucosa with maximum serum concentration reached within 17 minutes.
- Long plasma half-life of 24-48 hours with the active metabolite, nordiazepam, having a plasma half-life of 48-120 hours
- The oral solution may be administered via a gastrostomy tube. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.
- Available as: tablets (2 mg, 5 mg, 10 mg), oral solution (2 mg/5 mL, 5 mg/5 mL), rectal tubes (2.5 mg, 5 mg, 10 mg), and injection (5 mg/mL solution and 5 mg/ml emulsion).

Evidence: [1, 2, 6, 12, 19, 25, 52, 79-84]

## Diclofenac Sodium

### Use:

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

### Dose and routes

#### By mouth or rectum:

- **Child 6 months - 18 years:** initial dose of 0.3 mg/kg 3 times daily increasing if necessary to a maximum of 1 mg/kg 3 times daily (maximum 50 mg single dose).

#### By IM or IV infusion:

- **Child 2–18 years:** initial dose of 0.3 mg/kg 1–2 times daily; maximum of 150 mg/day and for a maximum of 2 days.

### Notes:

#### **Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease**

- Not licensed for use in children under 1 year; *suppositories* not licensed for use in children under 6 years except for use in children over 1 year for juvenile idiopathic arthritis; solid dose forms containing more than 25 mg not licensed for use in children; injection (for IM bolus or IV infusion only) not licensed for use in children.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk)
- 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 and infuse over 30-120 minutes
- Dispersible tablets may be administered via an enteral feeding tube. Disperse immediately before administration.
- Available as: tablets (25 mg, 50 mg, and 75 mg modified release), dispersible tablets (10 mg from a 'specials' manufacturer, 50 mg), modified release capsules (75mg and 100mg), injection (25 mg/mL Voltarol<sup>®</sup> for IM injection or IV infusion only), and suppositories (12.5 mg, 25 mg, 50 mg and 100 mg).

Evidence: [2, 6, 12, 43]

## Dihydrocodeine

### Use:

- Mild to moderate pain in patients known to be able to benefit.

### Dose and routes

By mouth or deep subcutaneous or intramuscular injection:

- **Child 1-4 years:** 500microgram/kg every 4-6 hours,
- **Child 4-12 years:** initial dose of 500microgram/kg (maximum 30 mg/dose) every 4-6 hours. Dose may be increased if necessary to 1 mg/kg every 4-6 hours (maximum 30 mg/dose),
- **Child 12-18 years:** 30 mg (maximum 50 mg by intramuscular or deep subcutaneous injection) every 4-6 hours,
- Modified release tablets used 12 hourly (use ½ of previous total daily dose for each modified release dose).

### Notes:

- Most preparations not licensed for children under 4 years.
- Relatively constipating compared with morphine / diamorphine and has a ceiling analgesic effect.
- Dihydrocodeine is itself an active substance, not a pro-drug like codeine.
- Oral bioavailability 20%, so probably equipotent with codeine by mouth (but opinion varies), twice as potent as codeine by injection.
- Time to onset 30 minutes, duration of action 4 hours for immediate release tablets.
- Side effects as for other opioids, plus paralytic ileus, abdominal pain, paraesthesia.
- Precautions: avoid or reduce dose in hepatic or renal failure.
- Available as: tablets (30 mg, 40 mg), oral solution (10 mg/5 mL), injection (CD) (50 mg/mL 1 mL ampoules) and m/r tablets (60 mg, 90 mg, 120 mg).

Evidence: [2, 5, 33, 43] EA, CC for injection

## Docusate

### Use:

- Constipation (faecal softener).

### Dose and routes

#### By mouth:

- **Child 6 months–2 years:** initial dose of 12.5 mg 3 times daily; adjust dose according to response,
- **Child 2–12 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 12–18 years:** initial dose 100mg/dose 3 times daily. Adjust as needed according to response up to 500 mg/day in divided doses.

#### By rectum:

- **Child 12–18 years:** 1 enema as single dose.

### Notes:

- Adult oral solution and capsules not licensed in children < 12 years.
- Oral preparations act within 1–2 days.
- Rectal preparations act within 20 mins.
- Mechanism of action is emulsifying, wetting and mild stimulant.
- 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: [2]

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

### Use:

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

### Dose and routes

#### *For nausea and vomiting*

#### By mouth:

- **> 1 month and body-weight  $\leq$  35 kg:** initial dose of 250microgram/kg 3–4 times daily increasing if necessary to 500microgram/kg 3-4 times daily. Maximum 2.4 mg/kg (or 80mg) in 24 hours,
- **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.

#### By rectum:

- **Body-weight 15–35 kg:** 30 mg twice a day,
- **Body-weight > 35 kg:** 60 mg twice a day.

#### *For gastro-oesophageal reflux and gastrointestinal stasis*

#### By mouth:

- **Neonate:** initial dose of 100microgram/kg 4–6 times daily before feeds. Dose may be increased, if necessary, to maximum of 300microgram/kg 4-6 times daily,
- **Child 1 month–12 years:** initial dose of 200microgram/kg (maximum single dose 10 mg) 3-4 times daily before food. Dose may be increased, if necessary, to 400microgram/kg 3-4 times daily. Maximum single dose 20 mg,
- **Child 12–18 years:** initial dose of 10 mg 3–4 times daily before food. Dose may be increased, if necessary, to 20 mg 3-4 times daily.

### Notes

- Domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- Domperidone is contraindicated in those
  - With conditions where cardiac conduction is, or could be, impaired
  - With underlying cardiac diseases such as congestive heart failure
  - Receiving other medications known to prolong QT interval (e.g. erythromycin, ketoconazole) or which are potent CYP3A4 inhibitors
  - With severe hepatic impairment
- This risk may be higher with daily doses greater than 30mg. Use at lowest effective dose.
- Not licensed for use in gastro-intestinal stasis; not licensed for use in children for gastro-oesophageal reflux disease.



- Reduced ability to cross blood brain barrier, so less likely to cause extrapyramidal side effects compared with metoclopramide.
- Promotes gastrointestinal motility so diarrhoea can be an unwanted (or useful) side effect.
- Not to be used in patients with hepatic impairment.
- For administration via an enteral feeding tube: Use the suspension formulation, although the total daily dose of sorbitol should be considered. If administering into the jejunum, dilute the suspension with at least an equal volume of water immediately prior to administration.
- Available as: tablets (10 mg), oral suspension (5 mg/5 mL), and suppositories (30 mg).

Evidence: [2, 3, 6, 12, 85-90]

## Entonox (nitrous oxide)

Use:

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

Dose and routes

By inhalation:

- **Child usually > 5 years old:** self-administration using a demand valve. Up to 50% in oxygen according to child's needs.

Notes:

- Is normally used as a light anaesthetic.
- 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.
- Prolonged use can cause megaloblastic anaemia.
- May be difficult to make available in hospice settings especially if needed infrequently, due to training, governance and supply implications.

Evidence: [2, 91]

## Erythromycin

### Use:

- Gastrointestinal stasis (motilin receptor agonist).

### Dose and routes

#### By mouth:

- **Neonate:** 3 mg/kg 4 times daily,
- **Child 1 month–18 years:** 3 mg/kg 4 times daily.

### Notes:

- Not licensed for use in children with gastrointestinal stasis.
- Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents.
- Erythromycin is a known inhibitor of the cytochrome P450 system and may increase the serum concentration of drugs which are metabolised by this system. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Particular care should be taken with medications known to prolong the QT interval of the electrocardiogram.
- Available as: tablets (250 mg, 500 mg) and oral suspension (125 mg/5 mL, 250 mg/5 mL, 500mg/5 mL).

Evidence: [2, 92, 93] SR

## Etamsylate

### Use:

- Treatment of haemorrhage, including surface bleeding from ulcerating tumours.

### Dose and routes

#### By mouth:

- **> 18 years:** 500 mg 4 times daily, indefinitely or until a week after cessation of bleeding.

### Notes:

- Not licensed for use with children with haemorrhage.
- Available as: tablets (500 mg).

Evidence: [1]

## Etoricoxib

### Uses:

- Anti-inflammatory analgesic; adjuvant for musculoskeletal pain

### Dose and route:

#### Oral:

- **Child 12-16 years:** initial dose of 30mg once daily. Dose may be increased as necessary and as tolerated to a maximum of 60mg once daily,
- **Child 16 years and older:** usual dose of 30-90mg once daily. Doses up to 120mg have been used on a short term basis in acute gouty arthritis in adults.

### Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.
- Etoricoxib is not licensed for use in children less than 16 years of age. The pharmacokinetics of etoricoxib in children less than 12 years of age have not been studied.
- Etoricoxib may mask fever and other signs of inflammation.
- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- Etoricoxib is contraindicated in those with: active peptic ulceration or active GI bleeding; severe hepatic or renal dysfunction; inflammatory bowel disease or congestive heart failure
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults COX-2 selective inhibitors, diclofenac (150mg daily) and ibuprofen (2.4g daily) are associated with an increased risk of thrombotic effects (e.g. myocardial infarction and stroke).
- All NSAIDs are associated with GI toxicity. In adults evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects with piroxicam and ketorolac associated with the highest risk and ibuprofen at low to medium dose with the lowest risk. Selective COX-2 inhibitors are associated with a lower risk of serious upper GI side-effects than non-selective NSAIDs. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur.
- Common (1-10% patients) AEs: alveolar osteitis; oedema/fluid retention; dizziness, headache; palpitations, arrhythmia; hypertension; bronchospasm; abdominal pain; constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer; ALT increased, AST increased; ecchymosis; asthenia/fatigue, flu-like disease
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Etoricoxib does NOT appear to inhibit or induce CYP isoenzymes. However, the main pathway of etoricoxib metabolism is dependent on CYP enzymes (primarily CYP3A4) so co-administration with drugs that are inducers or inhibitors of this pathway may affect the metabolism of etoricoxib.
- Etoricoxib is administered orally and may be taken with or without food. However, the onset of effect may be faster when administered without food.
- 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
- Available as: film coated tablets 30mg, 60mg, 90mg, 120mg. Tablets contain lactose

Evidence: [1, 94] SR EA

## Fentanyl

### Use:

- Step 2 WHO pain ladder once dose is titrated.

### Dose and routes

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

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

By transmucosal application (lozenge with oromucosal applicator),

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

By intranasal

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

By transdermal patch or continuous infusion:

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

By intravenous injection

- **Neonate or infant:** 1-2 micrograms/kg per dose slowly over 3-5 minutes; repeated every 2-4 hours,
- **Child:** 1-2 micrograms/kg per dose, repeated every 30-60 minutes.

By continuous intravenous infusion

- **Neonate or infant:** initial IV bolus of 1-2 micrograms/kg (slowly over 3-5 minutes) followed by 0.5-1 microgram/kg/hour,
- **Child:** initial IV bolus of 1-2 micrograms/kg (slowly over 3-5 minutes) followed by 0.5-1 microgram/kg/hour.
- 

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

morphine salt 30 mg daily  $\equiv$  fentanyl '12' patch

morphine salt 60 mg daily  $\equiv$  fentanyl '25' patch

morphine salt 120 mg daily  $\equiv$  fentanyl '50' patch

morphine salt 180 mg daily  $\equiv$  fentanyl '75' patch

morphine salt 240 mg daily  $\equiv$  fentanyl '100' patch

### Notes:

- Fentanyl patch should be changed every 72 hours and the site of application rotated.
- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.
- The injection solution can be administered by the intranasal route for doses less than 50 micrograms which is the lowest strength of nasal spray available.

- Injection solution could be administered drop wise (may be unpleasant) or using an atomiser device that A+E units use for intranasal diamorphine.
- The main advantage of fentanyl over morphine in children is its availability as a transdermal formulation.
- It can simplify analgesic management in patients with poor, deteriorating or even absent renal function.
- Avoid or reduce dose in hepatic impairment.
- It is a synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.
- Evidence that it is less constipating than morphine has not been confirmed in more recent studies [95].
- The patch formulation is not usually suitable for the initiation or titration phases of opioid management in palliative care since the patches represent large increments and because of the time lag to achieve steady state.
- The usefulness of lozenges in children is limited by the dose availability and no reliable conversion factor which also varies between preparations. Another caution is that opioid morphine approximate equivalence of the smallest lozenge (200 microgram) is 30 mg, meaning it is probably suitable to treat breakthrough pain only for children receiving a total daily dose equivalent of 180 mg morphine or more. Older children will often choose to remove the lozenge before it is completely dissolved, giving them some much-valued control over their analgesia. Note: the lozenge must be rotated in buccal pouch, not sucked. Unsuitable for pain in advanced neuromuscular disorders where independent physical rotation of lozenge is not possible.
- Pharmacokinetics of fentanyl intranasally are favourable but it is not always practical and/or well tolerated in children.

Available as fentanyl citrate:

- Intranasal spray (50 micrograms/metered spray, 100 micrograms/metered spray, 200 micrograms/metered spray Instanyl<sup>®</sup>). Also available as PecFent 100 microgram/metered spray and 400 microgram/metered spray.
- Lozenge with oromucosal applicator (200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1.2 mg, 1.6 mg Actiq<sup>®</sup>).
- Sublingual tablets (100, 200, 300, 400, 600 and 800micrograms (Abstral<sup>®</sup>)) and buccal tablets (Effentora<sup>®</sup> 100, 200, 400, 600 and 800micrograms; Breakyl<sup>®</sup> 200, 400, 600, 800 and 1200micrograms)
- Patches (12 microgram/hour, 25 microgram/hour, 50 microgram/hour, 75 microgram/hour, 100 microgram/hour).

Evidence: [2, 4, 5, 8, 77, 96-107] CC

## Fluconazole

### Use:

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

### Dose and routes

#### *Mucosal candidal infection*

By mouth or intravenous infusion:

- **Neonate under 2 weeks:** 3-6 mg/kg on first day then 3 mg/kg every 72 hours,
- **Neonate between 2-4 weeks:** 3-6 mg/kg on first day then 3 mg/kg every 48 hours,
- **Child 1 month–12 years:** 3-6 mg/kg on first day then 3 mg/kg (maximum 100 mg) daily,
- **Child 12–18 years:** 50 mg/day. Increase to 100 mg/day in difficult infections.

#### *Invasive candidal infections and cryptococcal infections*

By mouth or intravenous infusion:

- **Neonate under 2 weeks:** 6-12mg/kg every 72 hours
- **Neonate over 2 weeks:** 6-12mg/kg every 48 hours
- **Child 1 month – 18 years:** 6-12mg/kg (max.800mg) every 24 hours

#### *Prevention of fungal infections in immunocompromised patients*

By mouth or intravenous infusion

- **Neonate under 2 weeks:** 3-12mg/kg every 72 hours
- **Neonate over 2 weeks:** 3-12mg/kg every 48 hours
- **Child 1 month – 18 years:** 3-12mg/kg (max.400mg) every 24 hours

### Notes:

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

Evidence: [2, 12, 108, 109]

## Fluoxetine

### Use:

- Major depression.

### Dose and routes

#### By mouth:

- **Child 8–18 years:** initial dose 10 mg once a day. May increase after 1-2 weeks if necessary to a maximum of 20 mg once daily.

### Notes:

- Licensed for use in children from 8 years of age.
- Use with caution in children ideally with specialist psychiatric advice.
- Increased risk of anxiety for first 2 weeks.
- Onset of benefit 3-4 weeks.
- Consider long half-life when adjusting dosage. Do not discontinue abruptly.
- May also help for neuropathic pain and intractable cough.
- Suicide related behaviours have been more frequently observed in clinical trials among children and adolescents treated with antidepressants compared with placebo. Mania and hypomania have been commonly reported in paediatric trials.
- The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.
- Because the metabolism of fluoxetine, (like tricyclic antidepressants and other selective serotonin antidepressants), involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions.
- Must not be used in combination with a MAOI.
- Available as: capsules (20 mg) and oral liquid (20 mg/5 mL).

Evidence: [1, 2, 110-117]

## Gabapentin

### Use:

- Adjuvant in neuropathic pain.

### Dose and routes

#### By mouth:

- **Child >2years:**
  - Day 1 10 mg/kg as a single dose (maximum single dose 300 mg),
  - Day 2 10 mg/kg twice daily (maximum single dose 300 mg),
  - Day 3 onwards 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).
- **From 12 years:** the maximum daily dose can be increased according to response to a maximum of 3600 mg/day.

### Notes:

- Not licensed for use in children with neuropathic pain.
- Speed of titration after first 3 days varies between increases every 3 days for fast regime to increase every one to two weeks in debilitated children or when on other CNS depressants.
- No consensus on dose for neuropathic pain. Doses given based on doses for partial seizures and authors' experience.
- Dose reduction required in renal impairment. Consult manufacturer's literature.
- Very common (>1 in 10) side-effects: somnolence, dizziness, ataxia, viral infection, fatigue, fever
- Capsules can be opened but have a bitter taste.
- Available as: capsules (100 mg, 300 mg, 400 mg); tablets (600 mg, 800 mg) and oral solution 50mg in 5ml (Rosemont – however this product contains propylene glycol, acesulfame K and saccharin sodium and levels may exceed the recommended WHO daily intake limits if high doses are given to adolescents with low body-weight (39–50 kg)).

Evidence: [1, 2, 31, 33, 118-120] CC, SR



## Gaviscon®

### Use:

- Gastro-oesophageal reflux, dyspepsia, and heartburn.

### Dose and routes

#### By mouth:

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

### Gaviscon Liquid

- **Child 2-12 years:** 1 tablet or 5-10ml liquid after meals and at bedtime
- **Child 12-18 years:** 1-2 tablets or 10-20ml after meals and at bedtime

### Gaviscon Advance

- **Child 2-12 years:** 1 tablet or 2.5-5ml after meals and at bedtime (under medical advice only)
- **Child 12-18 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 – licensed for use from 2 years of age but age 2-6 years only on medical advice. Gaviscon Advance suspension and tablets licensed for use from 12 years of age; under 12 years on medical advice only.
- Gaviscon Infant should not to be used with feed thickeners, nor with excessive fluid losses, (e.g. fever, diarrhoea, vomiting).
- Gaviscon Liquid contains 3.1mmol sodium per 5ml; Gaviscon tablets contain 2.65mmol sodium and also contain aspartame. Gaviscon Advance Suspension contains 2.3mmol sodium and 1mmol potassium per 5ml and 2.25mmol sodium and 1mmol potassium per 5ml and also contain aspartame. Gaviscon Infant Sachets contain 0.92mmol sodium per dose (half dual sachet).
- Available as: Gaviscon liquid and tablets; Gaviscon Advance suspension and tablets; and infant sachets (comes as dual sachets, each half of dual sachet is considered one dose).

Evidence: [1-3]

## Glycerol (glycerin)

Use:

- Constipation.

Dose and routes

By rectum:

- **Neonate:** tip of a glycerol suppository (slice a small chip of a 1 g suppository with a blade),
- **Child 1 month–1 year:** 1 g infant suppository as required,
- **Child 1–12 years:** 2 g child suppository as required,
- **Child 12–18 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.
- Available as: suppositories (1 g, 2 g, and 4 g).

Evidence: [1, 2, 43] CC

## Glycopyrronium bromide

### Use:

- Control of upper airways secretion and hypersalivation.

### Dose and routes

#### By mouth:

- **Child 1 month-18 years:** initial dose of 40 microgram/kg 3–4 times daily. The dose may be increased as necessary to 100 microgram/kg 3-4 times daily. Maximum 2 mg/dose given 3 times daily.

#### Subcutaneous:

- **Child 1 month-12 years:** initial dose of 4 micrograms/kg 3 to 4 times daily. The dose may be increased as necessary to 10 microgram/kg 3-4 times daily. Maximum 200 microgram/dose given 4 times daily,
- **Child 12-18 years:** 200 micrograms every 4 hours when required.

#### Continuous subcutaneous infusion:

- **Child 1 month -12 years:** initial dose of 10 micrograms/kg/24 hours. The dose may be increased as necessary to 40 microgram/kg/24 hours (maximum 1.2 mg/24 hours),
- **Child 12-18 years:** initial dose of 600micrograms /24 hours. The dose may be increased as necessary to 1.2 mg/24 hours. Maximum recommended dose is 2.4 mg/24 hours.

### Notes:

- Not licensed for use in children for control of upper airways secretion and hypersalivation.
- Excessive secretions can cause distress to the child, but more often cause distress to those around him.
- Treatment is more effective if started before secretions become too much of a problem.
- Glycopyrronium does not cross the blood brain barrier and therefore has fewer side effects than hyoscine hydrobromide, which is also used for this purpose. Also fewer cardiac side effects.
- Slower onset response than with hyoscine hydrobromide or butylbromide.
- Oral absorption of glycopyrronium is very poor with wide inter-individual variation.
- For oral administration injection solution may be given or the tablets may be crushed and suspended in water. For administration via an enteral feeding tube, tablets may be dispersed in water. However the coarse dispersion settles quickly. Flush syringe and tube well to ensure all the dose is received.
- Administration by CSCI: good compatibility data available with other commonly used palliative agents.
- Available as: tablets (1 mg, 2 mg via an importation company as the tablets are not licensed in the UK); dosing often too inflexible for children, costly and can be difficult to obtain. Injection (200 microgram/mL 1mL ampoules) can also be used orally (unlicensed route). Oral solution can also be prepared extemporaneously from glycopyrronium powder and obtained from a 'specials' manufacturer.

Evidence: [2, 121-123]

## Haloperidol

### Use:

- Nausea and vomiting where cause is metabolic or in difficult to manage cases such as end stage renal failure.
- Restlessness and confusion.
- Intractable hiccups.
- Psychosis, hallucination

### Dose and routes

#### By mouth for *nausea and vomiting*:

- **Child 1 month–12 years:** initial dose of 50 microgram/kg/24 hours (initial maximum 3mg/24hrs) in divided doses. The dose may be increased as necessary to a maximum of 170 microgram/kg/24 hours in divided doses,
- **Child 12–18 years:** 1.5 mg once daily at night, increasing as necessary to 1.5 mg twice a day; maximum 5 mg twice a day.

#### By mouth for *restlessness and confusion*:

- **Child 1 month–12 years:** initial dose of 50 microgram/kg/24 hours (initial maximum 3mg/24hrs) in divided doses. The dose may be increased as necessary to a maximum of 170 microgram/kg/24 hours in divided doses
- **Child 12–18 years:** 10–20 microgram/kg every 8–12 hours; maximum 10 mg/day.

#### By mouth for *intractable hiccups*:

- **Child 1 month–12 years:** initial dose of 50 microgram/kg/24 hours (initial maximum 3mg/24hrs) in divided doses. The dose may be increased as necessary to a maximum of 170 microgram/kg/24 hours in divided doses
- **Child 12–18 years:** 1.5 mg 3 times daily.

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

- **Child 1 month–12 years:** initial dose of 25 microgram/kg/24 hours (initial maximum 1.5mg/24hrs). The dose may be increased as necessary to a maximum of 85 microgram/kg/24 hours,
- **Child 12–18 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.
- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for IM administration in adults; IV and SC administration off-label (all ages).
- Haloperidol can cause potentially fatal prolongation of the QT interval and torsades de pointes particularly if given IV (off-label route) or at higher than recommended doses. Caution is required if any formulation of haloperidol is given to patients with an underlying predisposition e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT interval. If IV haloperidol is essential, ECG monitoring during drug administration is recommended.
- Dosages for restlessness and confusion are often higher.

- Adult dosages can exceed 15 mg/24 hours in severe agitation.
- Oral doses are based on an oral bioavailability of ~50% of the parenteral route i.e. oral doses ~2x parenteral.
- Useful as long acting – once daily dosing is often adequate.
- Oral solutions may be administered via an enteral feeding tube.
- Available as: tablets (500 microgram, 1.5 mg, 5 mg, 10 mg, 20 mg), capsules (500 microgram), oral liquid (1 mg/mL, 2 mg/mL), and injection (5 mg/mL).

Evidence: [1, 2, 6, 12, 75, 124-128]

## 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 1–18 years:** 30 micrograms/kg per dose maximum 2mg per dose every 3-4 hours increasing as required. Modified release capsules with an initial dose of 4mg every 12 hours may be used from 12 years of age.

### By IV or SC injection:

- **Child 1-18 years:** initially 15 micrograms/kg per dose slowly over at least 2-3 minutes every 3-6 hours.
- Convert from oral (halve dose for equivalence).

### Notes:

- Hydrated morphine ketone effects are common to the class of mu agonist analgesics.
- Injection is not licensed in the UK. May be possible to obtain via a specialist importation company but as hydromorphone is a CD this is not a straightforward process.
- Oral form licensed for use in children from 12 years of age with cancer pain.
- Oral bioavailability 37-62% (wide inter-individual variation), onset of action 15 min for SC, 30 min for oral. Peak plasma concentration 1 hour orally. Plasma half life 2.5 hours early phase, with a prolonged late phase. Duration of action 4-5 hours.
- Potency ratios seem to vary more than for other opioids. This may be due to inter-individual variation in metabolism or bioavailability.
- Conversion of oral morphine to oral hydromorphone: divide morphine dose by 5-7
- Conversion of IV Morphine to IV hydromorphone: Divide morphine dose by 5-7
- Dosage discontinuation: after short-term therapy (7–14 days), the original dose can be decreased by 10–20% of the original dose every 8 hours increasing gradually the time interval. After long-term therapy, the dose should be reduced not more than 10–20% per week.
- Caution in hepatic impairment, use at reduced starting doses
- 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).

Evidence: CC, EA, [1, 2, 4, 5, 29, 33, 100, 101, 129, 130]

## Hyoscine butylbromide

### Use:

- Adjuvant where pain is caused by spasm of the gastrointestinal or genitourinary tract.
- Management of secretions, especially where drug crossing the blood brain barrier is an issue.

### Dose and routes

#### By mouth or IM or IV injection:

- **Child 1 month-4 years:** 300–500 micrograms/kg (maximum 5 mg/dose) 3–4 times daily,
- **Child 5-12 years:** 5-10 mg 3–4 times daily,
- **Child 12-18 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 5-12 years:** 30 mg/24 hours,
- **Child 12-18 years:** up to 60-80mg/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.
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- The injection solution may be given orally or via an enteral feeding tube. If the tube exits in the jejunum, consider using parenteral therapy. Injection solution can be stored for 24 hours in the refrigerator.
- IV injection should be given slowly over 1 minute and can be diluted with glucose 5% or sodium chloride 0.9%.
- Available as: tablets (10 mg) and injection (20 mg/mL).

Evidence: [1, 2, 12, 121, 123]

## Hyoscine hydrobromide

### Use:

- Control of upper airways secretions and hypersalivation.

### Dose and routes

#### By mouth or sublingual:

- **Child 2–12 years:** 10 micrograms/kg (maximum 300 micrograms single dose) 4 times daily,
- **Child 12–18 years:** 300 micrograms 4 times daily.

#### By transdermal route:

- **Child 1 month–3 years:** quarter of a patch every 72 hours,
- **Child 3–10 years:** half of a patch every 72 hours,
- **Child 10–18 years:** one patch every 72 hours.

#### By SC or IV injection or infusion:

- **Child 1 month–18 years:** 10 micrograms/kg (maximum 600 micrograms) every 4–8 hours or CSCI/IV infusion 40-60microgram/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.
- Apply patch to hairless area of skin behind ear.
- The patch can cause alteration of the pupil size on the side it is placed.
- Some specialists advise that transdermal patches should not be cut – however, the manufacturers of Scopoderm TTS patch have confirmed that it is safe to do this.
- Injection solution may be administered orally.
- Available as: tablets (150 micrograms, 300 micrograms), patches (releasing 1 mg/72hours), and injection (400 microgram/mL, 600 microgram/mL). An oral solution is available via a 'specials' manufacturer.

Evidence: [1, 2, 43, 121-123]



## Ibuprofen

### Use:

- Simple analgesic
- Pyrexia
- Adjuvant for musculoskeletal pain.

### Dose and routes

#### By mouth:

- **Neonate:** 5 mg/kg/dose every 12 hours
- **Child 1–3 months:** 5 mg/kg 3–4 times daily preferably after food,
- **Child 3–6 months:** 50 mg 3 times daily preferably after food; in severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 6 months–1 year:** 50 mg 3–4 times daily preferably after food; in severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 1–4 years:** 100 mg 3 times daily preferably after food. In severe conditions up to 30 mg/kg daily in 3–4 divided doses,
- **Child 4–7 years:** 150 mg 3 times daily, preferably after food. In severe conditions, up to 30 mg/kg daily in 3–4 divided doses.
- **Child 7–10 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 10–12 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 12–18 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 in rheumatic diseases, including idiopathic juvenile arthritis:*

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

#### *In systemic juvenile idiopathic arthritis:*

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

### Notes:

- **Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease.**
- Orphan drug licence for closure of ductus arteriosus in preterm neonate.
- Not licensed for use in children under 3 months of age or weight less than 5kg.
- Topical preparations and granules are not licensed for use in children.
- Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.
- 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 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.
- Available as: tablets (200 mg, 400 mg, 600 mg), capsule (300 mg MR), oral syrup (100 mg/5 mL), granules (600 mg/sachet), and spray, creams and gels (5%).

Evidence: [1-3, 12, 131],

## Ipratropium Bromide

Use:

- Wheezing/ Breathlessness caused by bronchospasm

Dose and routes

Nebulised solution

- **Child less than 1 year:** 62.5 micrograms 3 to 4 times daily,
- **Child 1-5 years:** 125-250 micrograms 3 to 4 times daily,
- **Child 5-12 years:** 250-500 micrograms 3 to 4 times daily,
- **Child over 12 years:** 500 micrograms 3 to 4 times daily.

Aerosol Inhalation

- **Child 1month-6 years:** 20 micrograms 3 times daily,
- **Child 6-12 years:** 20-40 micrograms 3 times daily,
- **Child 12-18 years:** 20-40 micrograms 3-4 times daily.

Notes

- Inhaled product should be used with a suitable spacer device, and the child/ carer should be given appropriate training.
- In acute asthma, use via an oxygen driven nebuliser.
- In severe acute asthma, dose can be repeated every 20-30 minutes in first two hours, then every 4-6 hours as necessary.
- Available as: nebuliser solution (250 micrograms in 1mL, 500 micrograms in 2mL), aerosol inhaler (20 microgram per metered dose).

Evidence: RE [2, 6]

## Ketamine

### Use:

- Adjuvant to a strong opioid for neuropathic pain.
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance

### Dose and routes

#### By mouth or sublingual:

- **Child 1 month – 12 years:** Starting dose 150 microgram/kg, as required or regularly 6 – 8 hourly; increase in increments of 150 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:** 10 mg as required or regularly 6 – 8 hourly; increase in steps of 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 40 microgram/kg/hour. Increase according to response; usual maximum 100 microgram/kg/hour. Doses up to 1.5 mg/kg/hour in children and 2.5 mg/kg/hour in adults have been reported.

### Notes:

- NMDA antagonist.
- Specialist use only.
- Not licensed for use in children with neuropathic pain.
- Higher doses (bolus injection 1–2 mg/kg, infusions 600 – 2700 microgram/kg/hour) used as an anaesthetic e.g. for short procedures.
- Sublingual doses should be prepared in a maximum volume of 2ml. The bitter taste may make this route unpalatable. Special preparations for sublingual use are available in UK.
- Enteral dose equivalents may be as low as 1/3 IV or SC dose because ketamine is potentiated by hepatic first pass metabolism. Other papers quote a 1:1 SC to oral conversion ratio (Ref: Benitez-Rosario)
- Agitation, hallucinations, anxiety, dysphoria and sleep disturbance are recognised side effects. These may be less common in children and when sub-anaesthetic doses are used.
- Ketamine can cause urinary tract symptoms- frequency, urgency, dysuria and haematuria. Consider discontinuing Ketamine if these symptoms occur. (new ref: Shahani, 2007; Chen )
- Caution in severe hepatic impairment, consider dose reduction.
- 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.
- 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.

Evidence: [101, 132-142] CC, EA

## Ketorolac

### Use:

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

### Doses and routes:

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

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

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

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

#### SC bolus

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

#### CSCI

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

### Notes:

- NSAID 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 gastroprotective drug especially if ketorolac is used for a prolonged period (outside the licensed indication). Use of ketorolac in adults carries a 15 times increased risk of upper gastrointestinal complications, and a 3 times increased risk compared with other nonselective NSAIDs.
- In adults all NSAID use can, to varying degrees, be associated with a small increased risk of thrombotic effects. The risk of cardiovascular effects secondary to NSAID use is undetermined in children, but in adults, ketorolac is associated with the highest myocardial infarction risk of all NSAIDs.
- Other potential adverse effects; Very common (>10% patients): headache, dyspepsia, nausea, abdominal pain; Common (1-10% patients): dizziness, tinnitus,

oedema, hypertension, anaemia, stomatitis, abnormal renal function, pruritus, purpura, rash, bleeding and pain at injection site. Risk of adverse effects likely to increase with prolonged use.

- Drug interactions include: anticoagulants (contraindicated as the combination may cause an enhanced anticoagulant effect); corticosteroids (increased risk of GI ulceration or bleeding); diuretics (risk of reduced diuretic effect and increase the risk of nephrotoxicity of NSAIDs); other potential nephrotoxic drugs.
- Onset of action IV/IM injection: 10-30mins; maximal analgesia achieved within 1-2 hours and median duration of effect 4-6 hours.
- SC injection can be irritant therefore dilute to the largest volume possible (0.9% NaCl suggested). Alkaline in solution so high risk of incompatibility mixed with acidic drugs. Some data of compatibility in 0.9% saline with diamorphine or oxycodone. Incompatibilities include with cyclizine, glycopyrronium, haloperidol, levomepromazine, midazolam and morphine.
- Available as: Injection 30mg/ml. Injection contains ethanol as an excipient.
- Oral 10mg tablets and injection 10mg/ml no longer available in the UK (discontinued early 2013 due to lack of demand).

Evidence: [1, 143-153]

## Lactulose

### Use:

- Constipation, faecal incontinence related to constipation
- Hepatic encephalopathy and coma.

### Dose:

#### *Constipation:*

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

- **Neonate:** 2.5 ml/dose twice a day
- **Child 1 month to 1 year:** 2.5 ml/dose 1-3 times daily,
- **Child 1 year to 5 years:** 5 ml/dose 1-3 times daily,
- **Child 5-10 years:** 10 ml/dose 1-3 times daily,
- **Child 10-18 years:** 15 ml/ dose 1-3 times daily.

#### *Hepatic encephalopathy:*

- **Child 12-18 years:** use 30-50 ml three times daily as initial dose. Adjust dose to produce 2-3 soft stools per day.

### Notes:

- Licensed for constipation in all age groups. Not licensed for hepatic encephalopathy in children.
- Side effects may cause nausea and flatus, with colic especially at high doses. Initial flatulence usually settles after a few days.
- Precautions and contraindications; Galactosaemia, intestinal obstruction. Caution in lactose intolerance.
- Use is limited as macrogols are often better in palliative care. However the volume per dose of macrogols is 5-10 times greater than lactulose and may not be tolerated in some patients.
- Sickly taste.
- Onset of action can take 36-48 hours.
- May be taken with water and other drinks.
- Relatively ineffective in opioid induced constipation: need a stimulant.
- 15 ml/ day is 14kcal so unlikely to affect diabetics.
- Does not irritate or directly interfere with gut mucosa.
- Available as oral solution 10 g/ 15 ml. Cheaper than Movicol (macrogol).

Evidence: [1, 2, 5, 6, 43, 154-156]

## Lansoprazole

### Uses:

- Gastro-oesophageal reflux disease; erosive oesophagitis; prevention and treatment of NSAID gastric and oesophageal irritation; treatment of duodenal and gastric ulcer.

### Dose and routes:

#### Oral

- **Child body weight <30kg:** 0.5-1mg/kg with maximum 15mg once daily in the morning
- **Child body weight >30kg:** 15-30mg 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<sup>+</sup>/K<sup>+</sup> ATPase of the parietal cells in the stomach. The inhibition is dose dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid.
- For optimal effect, the single daily dose is best taken in the morning.
- Lansoprazole should be taken at least 30 minutes before food as intake with food slows down the absorption and decreases the bioavailability.
- The dose may be increased if symptoms do not fully resolve (consider increasing the single daily dose or BD dosing).
- Studies in infants and children indicate they appear to need a higher mg/kg dose than adults to achieve therapeutic acid suppression.
- There is some anecdotal experience that Lansoprazole FasTabs may be halved to give a 7.5mg 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.
- 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 the swallowed. FasTabs can be swallowed whole with water or mixed with a small amount of water if preferred. FasTabs contain lactose and aspartame and should be used with caution in known PKU patients.
- For administration via a NG or gastrostomy tube, lansoprazole FasTabs can be dispersed in 10ml water and administered via an 8Fr NG tube without blockage. For

smaller bore tubes, dissolve the contents of a lansoprazole capsule in 8.4% sodium bicarbonate before administration. If the tube becomes blocked, use sodium bicarbonate to dissolve any enteric coated granules lodged in the tube. Lansoprazole less likely than omeprazole MUPS to cause blockage of small bore tubes.

- Available as 15mg and 30mg capsules and 15mg and 30mg FasTabs (Zoton<sup>(R)</sup>)

Evidence: [1, 2, 12, 157-170]

## Levomepromazine

### Use

- Broad spectrum antiemetic where cause is unclear, or where probably multifactorial.
- Second line if a specific antiemetic fails.
- Severe pain unresponsive to other measures - may be of benefit in a very distressed patient.
- Sedation for terminal agitation, particularly in end of life care.

### Dose and routes

#### *Used as antiemetic*

##### By mouth:

- **Child 2–12 years:** initial dose 50-100microgram/kg given once or twice daily. This dose may be increased as necessary and as tolerated not to exceed 1 mg/kg/dose (or maximum of 25mg/dose) given once or twice daily. ,
- **Child 12–18 years:** initial dose 3mg once or twice daily. This dose may be increased as necessary and as tolerated to a maximum of 25 mg once or twice daily.

##### By continuous IV or SC infusion over 24 hours:

- **Child 1 month–12 years:** initial dose of 100microgram/kg/24 hours increasing as necessary to a maximum of 400microgram/kg/24 hours. Maximum 25 mg/24 hours,
- **Child 12–18 years:** initial dose of 5 mg/24 hours increasing as necessary to a maximum of 25 mg/24 hours.

#### *Used for sedation*

##### By SC infusion over 24 hours:

- **Child 1 year–12 years:** initial dose of 350microgram/kg/24 hours (maximum initial dose 12.5 mg), increasing as necessary up to 3 mg/kg/24 hours,
- **Child 12–18 years:** initial dose of 12.5 mg/24 hours increasing as necessary up to 200 mg/24 hours.

### *Analgesia*

- In adults stat dose 12.5 mg/dose by mouth or SC. Titrate dose according to response; usual maximum daily dose in adults is 100 mg SC or 200 mg by mouth.

### 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.



- Some experience in adults with low dose used buccally as antiemetic (e.g. 1.5mg 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 that could increase or prolong both their therapeutic and/or adverse effects.
- Avoid, or use with caution, in patients with liver dysfunction or cardiac disease.
- Tablets may be halved or quartered to obtain smaller doses. Tablets/segments may be dispersed in water for administration via an enteral feeding tube.
- For SC infusion dilute with sodium chloride 0.9%. Water for injection may also be used. The SC dose is considered to be twice as potent as that administered orally.
- Available as: tablets (25mg) and injection (25mg/mL). A 6mg tablet is also available via specialist importation companies. An extemporaneous oral solution may be prepared.

Evidence: [1, 2, 5, 12, 171-173] CC, EA

## Lidocaine (Lignocaine) patch

### Use

- Localised neuropathic pain

### Dose and routes

#### Topical:

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

### Notes:

- Not licensed for use in children or adolescents under 18 years.
- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes.
- When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 hours) about  $3 \pm 2\%$  of the total applied lidocaine dose is systemically available and similar for single and multiple administrations.
- Maximum recommended number of patches in adults currently is 3 per application.
- The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product.
- The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
- A recent analysis by anatomic site of patch placement suggests that application to the head was tolerated less well compared with the trunk and extremities.

- Doses extrapolated from BNF 2012 March.
- Available as 700 mg/medicated plaster (5% w/v lidocaine).

Evidence: [1, 5, 174-179] CC, EA

## **Lomotil® (co-phenotrope)**

Use:

- Diarrhoea from non-infectious cause.

Dose and routes

By mouth:

- **Child 2–4 years:** half tablet 3 times daily,
- **Child 4–9 years:** 1 tablet 3 times daily,
- **Child 9–12 years:** 1 tablet 4 times daily,
- **Child 12–16 years:** 2 tablets 3 times daily,
- **Child 16–18 years:** initially 4 tablets then 2 tablets 4 times daily.

Notes:

- Not licensed for use in children < 4 years.
- Tablets may be crushed. For administration via an enteral feeding tube, tablets may be crushed and dispersed in water immediately before use. Young children are particularly susceptible to overdose and symptoms may be delayed and observation is needed for at least 48 hours after ingestion. Overdose can be difficult to manage with a mixed picture of opioid and atropine poisoning. Further, the presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals.
- Available only as tablets Co-Phenotrope (2.5 mg diphenoxylate hydrochloride and 25 microgram atropine sulphate).

Evidence: [1, 2, 180-182]

## Loperamide

### Use:

- Diarrhoea from non-infectious cause.
- Faecal incontinence

### Dose and routes

#### By mouth:

- **Child 1 month–1 year:** initial dose of 100microgram/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 1–12 years:** initial dose of 100microgram/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 12–18 years:** initial dose of 2 mg 2-4 times daily. Increase as necessary up to a maximum of 16 mg/day given in divided doses.

### Notes:

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

Evidence: [1, 2, 12, 183-185]

## Lorazepam

### Use

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

Dose and routes for all indications except status epilepticus:

By mouth:

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

Sublingual:

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

### Notes

- Not licensed for use in children for these indications other than status epilepticus.
- Tablets licensed in children over 5 years for premedication, injection not licensed in children less than 12 years except for treatment of status epilepticus
- Potency in the order of 10 times that of diazepam per mg as anxiolytic / sedative.
- Well absorbed sublingually with rapid onset of effect. There may however be variable absorption by this route with further variation possible depending on the formulation used; fast effect.
- Specific sublingual tablets are not available in the UK but generic lorazepam tablets (specifically Genus, PVL or TEVA brands) do dissolve in the mouth to be given sublingually.
- Tablets may be dispersed in water for administration via an enteral feeding tube.
- May cause drowsiness and respiratory depression if given in large doses.
- Caution in renal and hepatic failure.
- Available as tablets (1 mg, 2.5 mg) and injection (4 mg in 1mL).

Evidence: [2, 5, 12, 125, 186] CC, EA

## Macrogols: Movicol®

### Use

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

### Dose and routes (**Movicol® paediatric for those less than 12 years of age; Movicol<sup>(R)</sup> from 12 years of age**)

By mouth for constipation or prevention of faecal impaction:

- **Child under 1 year:** ½-1 sachet daily,
- **Child 1–6 years:** 1 sachet daily (adjust dose according to response; maximum 4 sachets daily),
- **Child 6–12 years:** 2 sachets daily (adjust dose according to response; maximum 4 sachets daily),
- **Child 12–18 years:** 1–3 sachets daily of **adult Movicol®**.

By mouth for faecal impaction:

- **Child under 1 year:** ½-1 sachet daily,
- **Child 1–5 years:** 2 sachets on first day and increase by 2 sachets every 2 days (maximum 8 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy,
- **Child 5–12 years:** 4 sachets on first day and increase by 2 sachets every 2 days (maximum 12 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy,
- **Child 12–18 years:** 4 sachets daily of adult Movicol® then increase by 2 sachets daily to a maximum of 8 adult Movicol 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 in those with impaired gag reflex, reflux oesophagitis or impaired consciousness
- Mix powder with water: Movicol® paediatric 60mL per sachet and adult Movicol® 125 mL per sachet.
- For administration via a feeding tube: Dissolve the powder in water as directed and flush down the feeding tube. Flush well after dosing.
- Macrogol oral powder is also available as alternative brands Laxido Orange<sup>(R)</sup>, Molaxole<sup>(R)</sup> but these preparations are licensed for use only from 12 years of age

Evidence: [1, 2, 12, 155, 187, 188]

## Melatonin

### Use:

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

### Dose and routes

#### By mouth:

- **Child 1 month-18 years:** initial dose 2–3 mg, increasing every 1–2 weeks dependent on effectiveness up to maximum 12 mg daily.

### Notes:

- Not licensed for use in children.
- Specialist use only.
- Some prescribers use a combination of immediate release and m/r tablets to optimise sleep patterns.
- Immediate release capsules may be opened and the contents sprinkled on cold food if preferred. Sustained release capsules may also be opened but the contents should not be chewed.
- Only licensed formulation in the UK is 2 mg m/r tablets (Circadin). Various unlicensed formulations, including an immediate release preparation are available from 'specials' manufacturers or specialist importing companies.

Evidence: [1, 2, 189-206] CC

## Methadone

**(WARNING: requires additional training for dosing)**

Use:

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

### **Caution:**

**Methadone should only be commenced by practitioners experienced in its use.**

This is due to wide inter-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, SC and IV injection:

- **Child 1-12 years:** 100-200 micrograms / kg every 4 hours for first 2-3 doses then every 6-12 hours (maximum dose 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 are required for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose is sufficient. Continuing on initial daily dose is likely to result in sedation within a few days, possible respiratory depression and even death.
- **Doses may need to be reduced by up to 50% 2-3 days after the initial, effective dose has been found to prevent adverse effects** due to tissue saturation and methadone accumulation. From then on increments in methadone dosing should be approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently).
- Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.
- For breakthrough pain, we would recommend using a short half-life opioid.

### **In opioid substitution/ rotation or switch**

*Caution:*

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

### Equianalgesic doses:

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

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

Other opioids should be considered first if switching from morphine due to unacceptable effects or inadequate analgesia.

Consultation with a pain clinic or specialist palliative-care service is advised

Ref [4]

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

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

It can be difficult to convert a short-half-life opioid to a methadone equivalent dose and vice versa. Current practice is usually to admit to a specialist inpatient unit for 5-6 days of regular treatment or titrate orally at home with close supervision.

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

- Approximate dose ratios for switching between oral dosage and parenteral / subcutaneous form 2:1 (oral: parenteral).
- Calculate the total daily dose of oral methadone and halve it (50%). This will be the 24hour parenteral / subcutaneous methadone dose.
- Seek specialist guidance if mixing with any other drug [207].
- If CSCI methadone causes a skin reaction, consider doubling the dilution and changing the syringe every 12 hours.
- Administer IV methadone slowly over 3-5 minutes.

#### **Notes:**

- Not licensed for use in children.
- Data on methadone in paediatric patients is limited; known to have wide inter-individual pharmacokinetic variation.
- Use methadone with caution, as methadone's effect on respiration lasts longer than analgesic effects.



- Side effects include: nausea, vomiting, constipation, dry mouth, biliary spasm, respiratory depression, drowsiness, muscle rigidity, hypotension, bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, dependence, confusion, urinary retention, ureteric spasm and hypothermia.
- Following concerns regarding methadone and sudden death from prolongation of QT interval or torsade de pointes (especially at high doses) it is recommended that patients have an ECG prior to initiation of treatment and regularly whilst on methadone, particularly if they have any risk factors or are having intravenous treatment of methadone.
- Opioid antagonists naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent individuals. Naloxone will also antagonize the analgesic, CNS and respiratory depressant effects of methadone.
- Methadone has the potential for a number of significant drug interactions. Drugs that induce cytochrome P450 3A4 enzymes (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, some HIV drugs) will increase the rate of metabolism of methadone and potentially lead to reduced serum levels. Drugs that inhibit the system (e.g. amitriptyline, ciprofloxacin, fluconazole) may lead to increased serum levels of methadone.
- Renal impairment: if severe (i.e. GFR <10 ml/min or serum creatinine >700 micromole/l) –reduce methadone dose by 50% and titrate according to response. Significant accumulation is not likely in renal failure, as elimination is primarily via the liver.
- As methadone has a long half-life, infusion of naloxone may be required to treat opioid overdose.
- Available as: linctus (2 mg/5 mL), mixture (1 mg/mL), solution (1 mg/mL, 5 mg/mL, 10 mg/mL, and 20 mg/mL), tablets (5 mg), and injection (10 mg/mL).

Evidence: [1, 2, 4, 5, 29, 43, 207-219]

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

A single dose may be sufficient. However repeat doses may be given with a usual administration schedule of a single dose every other day. Doses may be given with longer intervals, as per clinical need. Patients may receive 2 consecutive doses (24 hours apart) only when there has been no response (no bowel movement) to the dose on the preceding day. (1/3 to 1/2 of patients given methylnaltrexone have a bowel movement within 4 hours, without loss of analgesia).

### Notes:

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

Evidence: [1, 220-226]

## Metoclopramide

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

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

In children aged 1-18 years, metoclopramide should only be used as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and for treatment of established postoperative nausea and vomiting.

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

### Use

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

### Dose and routes

By mouth, IM injection, or IV injection (over at least 3 minutes):

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

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.
- Not licensed for continuous IV or SC infusion.
- Metoclopramide can induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. With metoclopramide, dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it.
- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.
- Oral liquid formulations should be given via a graduated oral syringe to ensure dose accuracy in children. The oral liquid may be administered via an enteral feeding tube.
- Can be irritant on SC administration; dilute well in 0.9% NaCl
- Available as: tablets (10 mg), oral solution (5 mg/5 mL) and injection (5 mg/mL).

Evidence: [1-3, 12, 43, 45, 47, 50, 85, 87, 227-231]

## Metronidazole topically

Use:

- Odour associated with fungating 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:

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

Evidence: [1, 2, 232]

## Miconazole oral gel

Use:

- Oral and intestinal fungal infection.

Dose and routes

By mouth:

*Prevention and treatment of oral candidiasis*

- **Neonate:** 1 mL 2-4 times a day smeared around inside of mouth after feeds,
- **Child 1 month–2 years:** 1.25 mL 4 times daily smeared around inside of mouth after food,
- **Child 2–18 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 – 18 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.
- Available as: oral gel (24 mg/mL in 15 g and 80 g tube).
- A buccal tablet of miconazole is now available. Indicated for the treatment of oropharyngeal candidiasis in immunocompromised adults, Loramyc<sup>(R)</sup> 50mg muco-adhesive buccal tablets should be applied to the upper gum just above the incisor tooth once daily for 7-14 days. Currently no experience in children but may be an option for adolescents.

Evidence: [2, 233]

## Midazolam

### Use:

- Status epilepticus and terminal seizure control.
- Breakthrough anxiety, e.g. panic attacks.
- Adjuvant for pain of cerebral irritation.
- Anxiety induced dyspnoea.
- Agitation at end of life.

### Dose and routes

By oral or gastrostomy administration for ***anxiety or sedation***:

- **1 month – 18 years:** 500 microgram/kg (maximum 20mg) as a single dose.

Buccal doses for ***acute anxiety***:

- **Any age:** 100 microgram/kg as a single dose (maximum initial dose 5 mg).

By SC or IV infusion over 24 hours ***for anxiety***:

- Dosages of 30-50% of terminal seizure control dose can be used to control anxiety, terminal agitation and terminal breathlessness.

Buccal doses for ***status epilepticus***:

- **Neonate:** 300 microgram/kg as a single dose, repeated once if necessary,
- **Child 1–3 months:** 300 microgram/kg (maximum initial dose 2.5 mg), repeated once if necessary,
- **Child 3 months–1 year:** 2.5 mg, repeated once if necessary,
- **Child 1–5 years:** 5 mg, repeated once if necessary,
- **Child 5–10 years:** 7.5 mg, repeated once if necessary,
- **Child 10–18 years:** 10 mg, repeated once if necessary.

By buccal or intranasal administration for ***status epilepticus***, should wait 10 minutes before repeating dose.

NB / In single dose for seizures, midazolam is twice as potent as rectal diazepam. For patients who usually receive rectal diazepam for management of status, consider an initial dose of buccal midazolam that is 50% of their usual rectal diazepam dose to minimise the risk of respiratory depression

By SC or IV infusion over 24 hours for ***terminal seizure control***:

- **Neonate (*seizure control*):** 150 microgram/kg IV loading dose followed by a continuous IV infusion of 60 microgram/kg/hour. Dose can be increased by 60 microgram/kg/hour every 15 minutes until seizure controlled (maximum dose 300 microgram/kg/hour),
- **Child 1 month – 18 years:** Initial dose 50 microgram/kg/hour increasing up to 300 microgram/kg/hour (maximum 100 mg/24 hours or 150 mg/24 hours in specialist units).

### 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.

- In single dose for sedation midazolam is 3 times as potent as diazepam, and in epilepsy it is twice as potent as diazepam. (Diazepam gains in potency with repeated dosing because of prolonged half life).
- Recommended SC/IV doses vary enormously in the literature. If in doubt, start at the lowest recommended dose and titrate rapidly.
- Onset of action by buccal and intranasal route 5-15 minutes. For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Onset of action by oral or gastrostomy route 10-30 minutes.
- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Midazolam has a short half life.
- High doses can lead to paradoxical agitation.
- Available as: oral solution (2.5 mg/mL unlicensed), buccal liquid (5 mg/mL Buccolam<sup>(R)</sup>), and injection 1mg/mL, 2mg/mL, 5mg/mL). Other oral and buccal liquids (e.g. Epistatus<sup>(R)</sup> 10mg/ml) are also available from 'specials' manufacturers or specialist importing companies (unlicensed). NOTE The buccal and oral formulations available may differ in strength – take care with prescribing.

Evidence: [2, 6, 78, 79, 81, 234-239]

## Morphine

### Use:

- Major opioid (WHO step 2).
- First line oral opioid for pain.
- Dyspnoea.
- Cough suppressant

### Dose and routes:

Opioid naïve patient: Use the following start doses. (The maximum dose stated applies to starting dose only).

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

By mouth or by rectum

- **Child 1–3 months:** initially 50 micrograms/kg every 4 hours, adjusted according to response
- **Child 3–6 months:** 100 micrograms/kg every 4 hours, adjusted according to response
- **Child 6–12 months:** 200 micrograms/kg every 4 hours, adjusted according to response
- **Child 1–12 years:** initially 200–300 micrograms/kg (initial maximum 5-10 mg) every 4 hours, adjusted according to response
- **Child 12–18 years:** initially 5–10 mg every 4 hours, adjusted according to response

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

- **Neonate:** initially 25 micrograms/kg every 6 hours adjusted to response,
- **Child 1-6 months:** initially 50-100 micrograms/kg every 6 hours adjusted to response,
- **Child 6 months-2 years:** initially 100 micrograms/kg every 4 hours adjusted to response,
- **Child 2-12 years:** initially 100 micrograms/kg every 4 hours adjusted to response, maximum initial dose of 2.5mg,
- **Child 12-18 years:** initially 2.5-5 mg every 4 hours adjusted to response (maximum initial dose of 20 mg/24 hours).

By continuous SC or IV infusion:

- **Neonate:** 5 micrograms/kg/hour adjusted according to response,
- **Child 1-6 months:** 10 micrograms/kg/hour adjusted according to response,
- **Child 6 months - 18 years:** 20 micrograms/kg/hour (maximum initial dose of 20 mg/24 hours) adjusted according to response.

Parenteral dose: 30-50% of oral dose if converting from oral dose of morphine

### *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.

- 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. The tube must be flushed well following dosing to ensure that the total dose is delivered. For sustained pain relief, use *MST Continus* sachets, dispersed in at least 10 mL of water. Flush the tube well following dosing to ensure that the total dose is delivered. Note that any granules left in the tube will break down over a period of time and a bolus of morphine will be delivered when the tube is next flushed; this has resulted in a reported fatality. Ensure that dose prescribed can be administered using whole sachets when possible. Use of *Zomorph* capsules opened to release the granules should be done with caution in children due to issues with dose accuracy and the granules should only be administered via an adult size gastrostomy.

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

- Tablets (10 mg, 20 mg, 50 mg)
- Oral solution (10 mg/5 mL (POM), 100 mg/5 mL)
- Modified release tablets and capsules 12 hourly (5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release suspension 12 hourly (20 mg, 30 mg, 60 mg, 100 mg, 200 mg).
- Modified release capsules 24 hourly (30 mg, 60 mg, 120 mg, 150mg, 200 mg).
- Suppositories (10 mg, 15 mg, 30 mg).
- Injection (10 mg/mL, 15 mg/mL, 20 mg/mL and 30 mg/mL)

Evidence: [1-3, 6, 12, 27, 29, 77, 100, 132, 240-259]



## Nabilone

### Use:

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

### Dose and routes

#### By mouth:

- **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. Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of treatment.
- For specialist use only.
- Available as: capsules (1 mg). Schedule 2 controlled drug.

Evidence: EA [1, 2, 5]

## Naloxone

### Use:

- Emergency use for reversal of opioid-induced respiratory depression or acute opioid overdose.
- Constipation when caused by opioids if methylnaltrexone not available and laxatives have been ineffective.

### Dose and routes

#### *Reversal of respiratory depression due to opioid overdose*

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

- **Neonate:** 10 micrograms/kg; if no response give a subsequent dose of 100 microgram/kg (then review diagnosis),
- **Child 1 month-12 years:** 10 micrograms/kg; if no response give a subsequent dose of 100 microgram/kg (then review diagnosis),
- **Child 12-18 years:** 400microgram-2 mg; if no response repeat at intervals of 2-3 minutes to maximum of 10 mg total dose (then review diagnosis).

By subcutaneous or intramuscular injection only if intravenous route not feasible

- As per intravenous injection but onset slower and potentially erratic.

By continuous intravenous infusion, adjusted according to response

- **Neonate:** Rate adjusted to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour).
- **Child 1 month-18 years:** Rate adjusted to response (initially, rate may be set at 60% of the initial resuscitative intravenous injection dose per hour).
- *The initial resuscitative intravenous injection dose is that which maintained satisfactory self ventilation for at least 15 minutes.*

#### *Opioid-induced constipation*

By mouth:

- In adults the following doses have been used: total daily dose oral naloxone = 20% of morphine dose; titrate according to need; maximum single dose 5 mg.

### Notes

- Potent opioid antagonist.
- Not licensed for use in children with constipation.
- Also see methylnaltrexone
- Naloxone acts within 2 minutes of IV injection and within 3-5 minutes of SC or IM injection.
- Although oral availability of naloxone is relatively low, be alert for opioid withdrawal symptoms, including recurrence of pain, at higher doses.
- Available as: injection (20 microgram/mL, 400microgram/ml, 1mg/ml).

Evidence: [2, 260, 261] EA

## Naproxen

### Uses:

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

### Dose and route:

- **Child 1 month -18 years:** 5mg/kg/dose BD (maximum 1g/ day)

Doses up to 10mg/kg BD (not exceeding 1g 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/1.73m<sup>2</sup> and in those with severe hepatic or heart failure.
- Generally naproxen is regarded as combining good efficacy with a low incidence of side-effects.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults COX-2 selective inhibitors, diclofenac (150mg daily) and ibuprofen (2.4g daily) are associated with an increased risk of thrombotic effects (e.g. myocardial infarction and stroke). Naproxen (in adults 1g daily) is associated with a lower thrombotic risk. The greatest risk may increase with dose and duration of exposure so the lowest effective dose should be used for the shortest possible duration of time.
- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects – piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac and naproxen are associated with intermediate risk and ibuprofen with the lowest risk. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur and can be significant.
- Other potential side-effects include headache, dizziness, vertigo, fluid retention and hypersensitivity reactions.
- The antipyretic and anti-inflammatory actions of naproxen may reduce fever and inflammation therefore reducing their utility as diagnostic signs.
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Naproxen is a substrate of CYP1A2 and CYP2C8/9 and can increase the plasma concentrations of methotrexate and lithium.
- 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. Enteric coated naproxen tablets should be swallowed whole and NOT be crushed or chewed. Naproxen should be taken with or after food.
- Available as: tablets 250mg and 500mg; enteric coated tablets 250mg and 500mg; oral suspension 25mg/ml (available only as a 'special' from specials manufacturers).

Evidence: [1, 2, 5, 12]

## Nystatin

### Use:

- Oral and perioral fungal infection.

### Dose and routes

#### By mouth:

- **Neonate:** 100 000 units 4 times a day,
- **Child 1 month–18 years:** 100 000 units 4 times a day.

### Notes:

- Licensed from 1 month of age for treatment. Neonates – nystatin is licensed for prophylaxis against oral candidosis at a dose of 1ml daily.
- Retain near lesions before swallowing.
- Administer after food or feeds.
- 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: [2, 108, 262]

## Octreotide

### Use:

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

### Dose and routes

#### *Bleeding from oesophageal varices*

By continuous intravenous or subcutaneous infusion

- **Child 1month-18 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.

#### *Nausea and vomiting, intestinal obstruction and intractable diarrhoea*

By continuous intravenous or subcutaneous infusion: doses up to 1 microgram/kg/hour have been used but experience is limited. Do not stop abruptly -discontinue at a reducing rate.

### Notes:

- Not licensed for use in children.
- Administration: for IV injection or infusion, dilute with sodium chloride 0.9% to a concentration of 10-50% (i.e. not less than 1:1 and not more than 1:9 by volume). For SC bolus injections, may be administered neat but this can be painful (this can be reduced if the ampoule is warmed in the hand to body temperature before injection). For SC infusion dilute with 0.9% NaCl.
- Avoid abrupt withdrawal.
- Available as: injection for SC or IV administration (50 micrograms/mL, 100 micrograms/mL, 200 micrograms/mL, 500 micrograms/mL). Also available as depot injection for IM administration every 28 days (10 mg, 20 mg and 30 mg Sandostatin Lar<sup>R</sup>). Recommend specialist palliative care advice.

Evidence: [2, 5, 43]

## Olanzapine

### Uses:

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

### Dose and route:

#### Oral:

#### *Psychoses / mania*

**Child <12 years and <25kg:** initial dose 2.5mg at night,

**Child <12 years and >25kg:** initial dose 2.5-5mg at night,

**Child 12-18 years:** initial dose 5mg at bedtime.

Increase gradually as necessary and as tolerated to a maximum of 20mg/day given usually as a single dose at night.

#### *Agitation/delirium*

**Child <12 years:** initial dose 1.25mg at night and PRN,

**Child 12-18 years:** initial dose 2.5mg at night and PRN.

Increase gradually as necessary and as tolerated to maximum 10mg/day.

#### *Nausea and vomiting; anorexia*

**Child <12 years:** initial dose 1.25mg (or 0.625mg if 2.5mg tablets can be cut into quarters) at night and PRN,

**Child 12-18 years:** initial dose 1.25-2.5mg at night and PRN.

Dose may be increased as necessary and as tolerated to a suggested maximum of 7.5mg/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 D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, 5-HT<sub>2A</sub>, 5HT<sub>3</sub>, 5HT<sub>6</sub>, histamine-1 and muscarinic receptors.
- Olanzapine has 5x the affinity for 5HT<sub>2</sub> receptors than for D<sub>2</sub> receptors resulting in fewer extrapyramidal side-effects.
- Activity of olanzapine at multiple receptors is similar to methotrimeprazine and therefore it has a potential role in the treatment of nausea and vomiting refractory to standard medication.
- Use with caution in those with cardiovascular disease or epilepsy (and conditions predisposing to seizures).
- 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 and neutropenia. Hyperglycaemia and sometime 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. Some anecdotal experience that 5mg orodispersible tablets may be halved to give a 2.5mg 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 5mg, 10mg, 15mg, 20mg.

Evidence: [1, 2, 263-276]

## Omeprazole

### Use:

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

### Dose and routes

#### By mouth:

- **Neonate:** 700 microgram/kg once daily; increase if necessary to a maximum of 1.4 mg/kg once daily (max dose: 2.8mg/kg once daily),
- **Child 1 month–2 years:** 700 microgram/kg once daily; increase if necessary to a maximum of 3 mg/kg once daily (max: 20mg once daily)
- **Child body weight 10–20 kg:** 10 mg once daily; increase if necessary to a maximum of 20 mg once daily.
- **Child body weight > 20 kg:** 20 mg once daily; increase if necessary to a maximum of 40 mg once daily.

#### Intravenous (by injection over 5minutes or by infusion over 20-30 minutes)

- **Child 1 month -12 years:** initially 500 micrograms/kg (max: 20 mg) once daily, increased, if necessary to 2 mg/kg (max: 40 mg) once daily,
- **Child 12-18 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.
- Injection not licensed for use in children under 12 years.
- Many children with life limiting conditions have gastro-oesophageal reflux disease and may need to continue with treatment long term.
- Can cause agitation.
- Occasionally associated with electrolyte disturbance.
- 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). .
- Available as: MUPS tablets (10 mg, 20 mg, 40 mg), capsules (10 mg, 20 mg, 40 mg), intravenous injection (40 mg) and intravenous infusion (40 mg), oral suspension available as special order (10 mg/5 mL).

Evidence: [1-3, 12, 170, 277-279]



## Ondansetron

### Use:

- Antiemetic, if vomiting caused by chemotherapy or radiotherapy.
- May have a use in managing opioid induced pruritus.

### Dose and routes

#### *Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting*

- By intravenous infusion over at least 15 minutes

Child 6 months–18 years: *either* 5 mg/m<sup>2</sup> 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–18 years:

Body surface area less than 0.6 m<sup>2</sup> *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<sup>2</sup> – 1.2m<sup>2</sup> *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<sup>2</sup> *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 slow intravenous injection over 2-5 minutes or by intravenous infusion over 15 minutes

- **Child 1-18 years:** 100-150microgram/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.
- 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. Avoid ondansetron in patients with congenital long QT syndrome.

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.
- Repeat IV doses of ondansetron should be given no less than 4 hours apart.
- Can cause constipation and headache.
- 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.
- Available as: tablets (4 mg, 8 mg), oral lyophilisate (4 mg, 8 mg), oral syrup (4 mg/5 mL), injection (2 mg/mL, 2 mL and 4 mL amps).

Source: [2, 6, 44, 75, 228, 280-282]

## Oxycodone

### Use:

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

### Dose and routes

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

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

### By mouth:

#### Conversion

- Oral Morphine 1.5: Oral Oxycodone 1,  
i.e. 15mg Morphine: 10mg Oxycodone
- **Child 1 - 12 months:** initial dose 50-125 micrograms/kg every 4-6 hours,
- **Child 1 - 12 years:** initial dose 125-200 micrograms/kg (maximum single dose 5 mg) every 4 -6 hours,
- **Child 12-18 years:** starting dose 5 mg every 4-6 hours.
- Titrate as for morphine: Increase dose if necessary according to severity of pain.
- **m/r tablets Child 8-12 years:** initial dose 5 mg every 12 hours, increased if necessary,
- **m/r tablets Child 12-18 years:** initial dose 10 mg every 12 hours, increased if necessary.

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

#### Conversion:

- Oral to IV or SC Oxycodone single bolus dose injection: Divide the oral Oxycodone dose by 1.5.
- Oral to a continuous subcutaneous infusion of Oxycodone over 24 hours: Divide the total daily dose of oral Oxycodone by 1.5.
- SC/IV Morphine to SC/IV Oxycodone ratio is approximately 1:1. i.e. use same dose.
- Reason behind odd conversion ratio is bio-availability and rounding factors for safety.

### Notes:

- Opioid analgesic.
- Not licensed for use in children.
- 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 candidate for opioid substitution.
- Caution in hepatic or renal impairment.
- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with WFI, 0.9% sodium chloride or 5% glucose.
- Oxycodone liquid may be administered via an enteral feeding tube.
- Controlled drug schedule 2.

- Available as: tablets and capsules (5 mg, 10 mg, 20 mg), liquid (5 mg/5 ml, 10 mg/ml) and m/r tablets (5 mg, 10 mg, 15mg, 20 mg, 30mg, 40 mg, 80 mg, 120mg), injection (10 mg/ml and 50 mg/ml).

Evidence: [1, 2, 5, 12, 97, 283-287]

## Oxygen

### Use

- Breathlessness caused by hypoxaemia.
- Palliative care for symptom relief including recognition of potential placebo effect.

### 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 rate and/or type of mask. 28% oxygen is usually recommended for continuous oxygen delivery.

### Notes:

- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Where self-report is not possible observation of the work of breathing is a more reliable indicator of breathlessness.
- Frequent or continuous measurement of oxygen saturations may lead to an over-reliance on technical data and distract from evaluation of the child's overall comfort, symptom relief and wellbeing.
- Target oxygen saturations 92 – 96% may be appropriate in acute illness but are not necessarily appropriate for palliative care. More usual target oxygen saturations are above 92% in long-term oxygen therapy and 88-92% in children at risk of hypercapnic respiratory failure. Lower saturation levels may be tolerated in children with cyanotic congenital heart disease.
- It is important to be clear about the overall aims of oxygen treatment and realistic saturation levels for an individual child, as this will affect decisions about target oxygenation.
- In cyanotic congenital heart disease, oxygen has little effect in raising SaO<sub>2</sub> and is not generally indicated, although the degree of polycythaemia may be reduced. Pulmonary hypertension, in the early stages, may respond to oxygen, so it may be appropriate in the palliative care setting.
- Moving air e.g. from a fan maybe equally effective in reducing the sensation of breathlessness when the child is not hypoxaemic.
- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions. However continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.
- Oxygen administration via a mask can be claustrophobic.
- 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](http://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: [1, 2, 288-292]

## Pamidronate (Disodium)

Use:

- Adjuvant analgesic for bone pain caused by metastatic disease.
- Adjuvant analgesic for bone pain in neurological and neuromuscular disorders, particularly due to osteopaenia or osteoporosis.
- Tumour-induced hypercalcaemia.
- Treatment of secondary osteoporosis to reduce fracture risk.

NB Evidence base is poor but growing for these uses in children. Seek specialist advice before use.

Dose and routes

*For bone pain (metastatic bone disease or osteopenia); secondary osteoporosis:*

An effect on pain should be seen within 2 weeks, but may need a year before definitive assessment. Continue dosing for as long as effective and tolerated or until substantial decline in performance status.

By IV infusion

- 1mg/kg as a single dose infused over 4-6 hours repeated monthly as required; concentration not exceeding 60mg in 250ml.
- OR
- 1mg/kg infused over 4-6 hours on 3 consecutive days and repeated every 3 months as required; concentration not exceeding 60mg in 250ml.

*For malignant hypercalcaemia: (Seek specialist advice)*

By IV infusion

- 1 mg/kg infused over 6 hours; concentration not exceeding 60mg in 250ml. Then repeated as indicated by corrected serum calcium.

Notes:

- Not licensed for use in children. Well tolerated by children, but long term effects unknown.
- 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.
- Oral risedronate and oral alendronate limited use for these indications due to poor and variable bio-availability.
- If the IV route is unavailable, bisphosphonates can be administered by CSCI over 12-24hours, together with SC hydration.
- Many bisphosphonates are available in different formulations, including oral, although absorption tends to be poor by the oral route and further reduced by food or fluids other than plain water.
- Caution: monitor renal function and electrolytes; ensure adequate hydration.
- Prolonged hypocalcaemia and hypomagnesaemia may occur with concurrent use of aminoglycoside and a bisphosphonate. Consider calcium and vitamin D oral supplements to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases and at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight).
- Risk of renal impairment is increased by concurrent use with other nephrotoxic drugs.
- Risk of atypical femoral fractures, and of osteonecrosis especially of jaw if pre-existing pathology. Recommend dental check pre administration.
- Anecdotal risk of iatrogenic osteopetrosis with prolonged use (if prolonged use is likely, precede with DEXA scan and investigation of calcium metabolism).
- Available as: injection vials for infusion of various volumes, at 3mg/ml, 6mg/ml, 9mg/ml, 15mg/ml.

Evidence: CC, EA [1, 5, 293-300]

## Paracetamol

### Use:

- Mild to moderate pain,
- 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 75-150mg/kg/day (ingestion of over 150mg/kg/day is regarded as a definite risk of toxicity).

### Oral

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

### Rectal:

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

### IV: as infusion over 15 minutes

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

Notes:

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

Evidence: [1-3, 6, 12, 301-305] SR



## Paraldehyde (rectal)

### Use:

- Treatment of prolonged seizures and status epilepticus.

### Dose and route:

By rectal administration (**dose shown is for premixed enema 50:50 with olive oil**)

- **Neonate:** 0.8 mL/kg as a single dose
- **1 month -18 years:** 0.8 mL/kg (maximum 20mL) as a single dose.

### Notes:

- Rectal administration may cause 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: [2, 6, 306-312] CC, SR

## Phenobarbital

### Use:

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

### Dose and routes

*Status epilepticus / terminal seizures / agitation*

**Loading dose:** Oral, intravenous or subcutaneous injection:

All ages: 20 mg/kg/dose (maximum 1g) administered over 20 minutes if by IV or SC injection (but see notes below)

Subcutaneous or intravenous injection or infusion:

- **Neonates for control of ongoing seizures:** 2.5-5 mg/kg once or twice daily as maintenance,
- **Child 1 month- 12years:** 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 12-18 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–12 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 12–18 years:** 60–180 mg once a day.

Notes:

- Not licensed for agitation in end of life care.
- Single loading dose is required for initiation of therapy; administer via enteral route if possible. Loading dose can be administered intravenously over 20 minutes or as a slow subcutaneous loading dose however the volume of resultant solution will limit the rate at which a subcutaneous bolus can be administered.
- Loading dose essential to reach steady state quickly and avoid late toxicity due to accumulation.
- For patients already on oral phenobarbital but needing parenteral treatment, doses equivalent to the patient's usual total daily dose of oral phenobarbital can be used.
- Elimination half life of 2 - 6 days in adults, 1 - 3 days in children.
- Phenobarbital induces various enzymes of the CYP450 system and thus may reduce the plasma concentrations of concomitant drugs that are metabolised by this system
- Tablets may be crushed for administration if preferred.
- Use a separate site to commence subcutaneous infusion. SC bolus injections should be avoided because they can cause tissue necrosis due to the high pH.
- It is essential to dilute the injection in 10 times the volume of water for injection before intravenous or subcutaneous injection (i.e. to concentration of 20 mg/mL).
- Available as: tablets (15 mg, 30 mg, 60 mg), oral elixir (15 mg/5 mL) and injection (15mg/mL, 60mg/mL and 200 mg/mL). The licensed oral elixir of 15mg in 5mL contains alcohol 38% and it is preferable to obtain an alcohol free oral liquid via one of the specials manufacturers.

Evidence: [2, 3, 81, 313, 314]

## Phenytoin

### Use:

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

### Dose

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

### Oral or slow IV injection:

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

### Status epilepticus, acute symptomatic seizures:

#### Slow IV injection or infusion:

- **Neonate:** 20 mg/kg loading dose over at least 20 minutes, then 2mg/kg/dose (over 30 minutes) every 8-12 hours as a usual maintenance dose in first week of life. Adjust according to response and older babies may need higher doses. After the first dose, oral doses usually as effective as intravenous in babies over 2 weeks old.
- **1 month to 12 years:** 20 mg/kg loading dose over at least 20 minutes, then 2.5-5 mg/kg twice daily usual maintenance dose,
- **12 to 18 years:** 20 mg/kg loading dose over at least 20 minutes, then up to 100mg (over 30 minutes) 3 to 4 times daily usual maintenance dose.

### Notes:

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

- Avoid abrupt withdrawal.
- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- Before and after administration, flush intravenous line with Sodium Chloride 0.9%.
- For *intravenous injection*, give into a large vein at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute).
- For *intravenous infusion*, dilute to a concentration not exceeding 10 mg/mL with Sodium Chloride 0.9% and give into a large vein through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation.
- Prescriptions for oral preparations should include brand name and be of consistent preparation type, to ensure consistency of drug delivery.
- Preparations containing phenytoin sodium are **not** bioequivalent to those containing phenytoin base (such as *Epanutin Infatabs*® and *Epanutin*® suspension); 100 mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92 mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma phenytoin concentration monitoring is recommended.
- Bioavailability may be reduced unpredictably by enteral feeds and/or nasogastric tube feeds, so flush with water to enhance absorption, interrupt enteral feeding for at least 1-2 hours before and after giving phenytoin, and maintain similar timings and regimes from day to day.
- Available as tablets (phenytoin sodium 100 mg, generic), capsules (*Epanutin*<sup>R</sup> phenytoin sodium 25 mg, 50 mg, 100 mg, 300 mg), *Epanutin*<sup>R</sup> Infatabs (chewable tablets of phenytoin base 50 mg), oral suspension (*Epanutin*<sup>R</sup> phenytoin base 30 mg/5 mL, and 90 mg/5 mL phenytoin base available as an 'unlicensed special'), and injection (phenytoin sodium 50mg/ml generic)

Evidence: [2, 3, 5, 6, 12, 34, 286, 315-319], SR, CC

## Phosphate (rectal enema)

Use:

- Constipation refractive to other treatments.

Dose and routes:

By rectal enema:

- **Child 3–7 years:** 45-65 mL once daily,
- **Child 7-12 years:** 65-100 mL once daily,
- **Child 12–18 years:** 100-128 mL once daily.

Notes

- Maintain good hydration and watch for electrolyte imbalance
- Contraindicated in acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption).
- Use only after specialist advice.
- Available as Phosphate enema BP formula B in 128 mL with standard or long rectal tube (NB alternative Fleet<sup>R</sup> Ready to Use enema requires slightly different dosing: 40-60ml for age 3-7y, 60-90 ml for age 7-12 y and 90-118 ml for age 12-18y).

Evidence: [1, 2, 320, 321], CC, SR

## Promethazine

### Use:

- Sleep disturbance.
- Mild sedation
- Antihistamine.
- Can also be used to treat nausea and vomiting, and vertigo.

### Dose and routes (for promethazine hydrochloride)

#### By mouth:

#### *Symptomatic relief of allergy:*

- **Child 2–5 years:** 5 mg twice daily *or* 5–15 mg at night,
- **Child 5–10 years:** 5–10 mg twice daily *or* 10–25 mg at night,
- **Child 10–18 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 2–5 years:** 15-20 mg at night,
- **Child 5–10 years:** 20-25 mg at night,
- **Child 10–18 years:** 25-50 mg at night.

#### *Nausea and vomiting (particularly in anticipation of motion sickness)*

- **Child 2–5 years:** 5 mg twice daily,
- **Child 5–10 years:** 10 mg twice daily,
- **Child 10–18 years:** 20–25 mg twice daily.

### Notes:

- Antimuscarinic phenothiazine antihistamine also with D2 antagonist activity.
- Not for use in under 2 years due to risk of fatal respiratory depression.
- Note drug interactions, particularly causing increased antimuscarinic and sedative effects.
- Caution in epilepsy.
- Can be effective for up to 12 hours. Drowsiness may wear off after a few days of treatment.
- For use by feeding tube: the elixir is slightly viscous so can be mixed with an equal volume of water 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 (25mg/ml). (Promethazine teoclate tablets also available, 25mg, licensed for nausea, vomiting and labyrinthine disorders. Dosing slightly different).

Evidence: [2, 12, 39], CC, EA

## Quinine Sulphate

### Use:

- Leg cramps.

### Dose and routes

#### By mouth:

- Not licensed or recommended for children as no experience.
- **Adult dose:** quinine sulphate 200mg at bedtime, increased to 300mg if necessary.

### Notes:

- Not licensed for use in children for this condition.
- Moderate evidence indicates it to be more effective than placebo in reducing frequency and intensity of cramp.
- Regulatory agencies consider that, given that alternatives to quinine are available, the risks associated with its use are unacceptably high. Rare but serious side effects include thrombocytopenia and haemolytic-uraemic syndrome. Also very toxic in overdose, and has serious interactions with warfarin and digoxin. Therefore MHRA advises that quinine should only be used if 4 criteria are all met: treatable causes have been ruled out, non pharmacological measures have failed, cramps regularly cause loss of sleep, and they are very painful or frequent. Patients should be monitored for signs of thrombocytopenia in the early stages of treatment.
- If used, treatment should be discontinued after 4 weeks if ineffective, and interrupted every 3 months to re-evaluate benefit.
- Available as: tablets (200 mg quinine sulphate).

Evidence: [1, 322, 323], EA

## Ranitidine

### Use:

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

### Dose and routes

#### By mouth:

- **Neonate:** 2–3 mg/kg 3 times daily (absorption unreliable),
- **Child 1–6 months:** 1 mg/kg 3 times daily increasing if necessary to maximum 3 mg/kg 3 times daily,
- **Child 6 months–3 years:** 2–4 mg/kg twice a day,
- **Child 3–12 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 2.5mg/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 2mg/kg 8 hourly as variable first pass metabolism affects uptake),
- **Child 1 month–18 years:** 1 mg/kg (max. 50 mg) every 6–8 hours (may be given as an intermittent infusion at a rate of 25 mg/hour).

### Notes:

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

Evidence: [1-3, 12, 324-327]

## Risperidone

### Use:

- Dystonia and dystonic spasms refractory to first and second line treatment.
- Psychotic tendency / crises in Battens disease.
- Has anti-emetic activity (some experience in refractory nausea and vomiting in adults; not evaluated in children).
- Treatment of mania or psychosis under specialist supervision.

### Dose and routes

#### Oral:

- **Child 5 - 12 years (weight 20 - 50 kg):** 250 microgram once daily; increasing, if necessary, in steps of 250 microgram on alternate days to maximum of 750 microgram daily.
- **Child 12 years or over (>50 kg):** 500 microgram once daily; increasing in steps of 500 microgram on alternate days to maximum of 1.5 mg daily.
  - In Juvenile Battens Disease, may need 500microgram daily increasing to 1.5mg TDS during crises with hallucinations: this dose can be reduced or stopped as symptoms settle (episodes usually last 1-6 weeks).

### Notes

- Not licensed for use in children for these indications. 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.
- 99% bioavailable. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half life 24hours. Duration of action 12-48hours.
- Caution in epilepsy and cardiovascular disease; extrapyramidal symptoms less frequent than with older antipsychotic medications; withdraw gradually after prolonged use. Risperidone can cause significant weight gain.
- Initial and subsequent doses should be halved in renal or hepatic impairment.
- Tablets disintegrate in water within 5 minutes for easy administration via enteral feeding tubes. The oral liquid is simple to administer via feeding tube.
- Available as: tablets (500microgram, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg), orodispersible tablets (500microgram, 1 mg, 2 mg, 3 mg, 4 mg), Liquid 1 mg/mL.

Evidence: CC [2, 12, 124, 328, 329]



## Salbutamol

### Use:

- Wheezing/ breathlessness caused by bronchospasm.
- Also used in hyperkalemia, for prevention and treatment of chronic lung disease in premature infants, and sometimes in muscular disorders or muscle weakness (seek specialist advice, not covered here).

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

(NB see separate detailed guidance in standard texts for use in acute asthma).

### Aerosol Inhalation:

- **Child 1 month-18years:** 100-200 micrograms (1-2 puffs) for persistent symptoms up to four times a day.

### Nebulised solution:

- **Neonate:** 1.25-2.5 mg up to four times daily,
- **Child 1 month-18years:** 2.5-5 mg up to four times daily.

### Oral preparations: (but use by inhalation preferred for treatment of bronchospasm)

- **Child 1 month-2 years:** 100 micrograms/kg (max. 2 mg) 3-4 times daily
- **Child 2-6 years:** 1-2 mg 3-4 times daily
- **Child 6-12 years:** 2 mg 3-4 times daily
- **Child 12-18 years:** 2-4 mg 3-4 times daily

### Notes

- Salbutamol is not licensed for use in hyperkalaemia; syrup and tablets are not licensed for use in children less than 2 years; modified-release tablets are not licensed for use in children less than 3 years; 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.
- Salbutamol has not been shown to be effective in children less than 2 years, presumably due to the immaturity of the receptors; ipratropium may be more helpful in those less than 1-2 years.
- For an acute episode, many paediatricians now advise multi-dosing of salbutamol 100 microgram up to 10 times, via a spacer where practicable for the patient instead of a nebuliser.
- 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.
- 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 nebulisers are intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile 0.9% 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. Also available as salbutamol tablets (costly) 2 mg and 4mg and modified release capsules 4mg and 8mg, and as oral solution 2mg/5ml . Preparations for injection (500micrograms/ml) and intravenous infusion (1mg/ml) are also available.

Evidence: [1-3, 330, 331]

## Senna

Use:

- Constipation

Dose and routes

By mouth:

Initial doses which can be adjusted according to response and tolerance

- **Child 1 month –2 years:** 0.5 mL/kg (maximum 2.5 mL) of syrup once a day,
- **Child 2 –6 years:** 2.5-5 mL of syrup a day,
- **Child 6–12 years:** 5-10 mL a day of syrup or 1-2 tablets at night or 2.5-5 mL of granules,
- **Child 12–18 years:** 10-20 mL a day of syrup or 2-4 tablets at night or 5-10 mL of granules.

Notes:

- Syrup is not licensed for use in children < 2 years and tablets/ granules are not licensed for use in children <6 years.
- Stimulant laxative.
- Onset of action 8-12 hours.
- Initial dose should be low then increased if necessary.
- Doses can be exceeded on specialist advice.
- Granules can be mixed in hot milk or sprinkled on food.
- Oral liquid may be administered via an enteral feeding tube.
- Available as: tablets (7.5 mg sennoside B), oral syrup (7.5 mg/5 mL sennoside B) and granules (15 mg/5 mL sennoside B).

Evidence: [2, 6, 12, 87]

## Sodium Citrate

### Use:

- Constipation where osmotic laxative indicated.

### 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 3–18 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 3–18 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–18 years: 5 mL as a single dose (insert only half nozzle length in child under 3 years).

### Notes

- For under 3 years, insert only half nozzle length.
- Available as: micro-enema (5 mL).

Evidence: [1, 2]

## Sodium Picosulfate

### Use:

- Constipation.

### Dose and routes:

#### By mouth:

- **Child 1month–4 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 4–18 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 of all ages; capsules are not licensed for use in children less than 4 years of age.
- Acts as a stimulant laxative.
- Onset of action 6-12 hours.
- 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 prior to administration. 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: [1, 2, 12]

## 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.

### Dose and route:

#### Oral

*Stress ulcer prophylaxis, prophylaxis against bleeding from oesophageal or gastric varices*

- **Child 1 month-2 years:** 250 mg four to six times daily,
- **Child 2-12 years:** 500 mg four to six times daily,
- **Child 12-15 years:** 1 g four to six times daily,
- **Child 15-18 years:** 1 g six times daily (maximum 8 g/day).

*Oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration*

- **Child 1 month -2 years:** 250 mg four to six times daily,
- **Child 2-12 years:** 500 mg four to six times daily,
- **Child 12-15 years:** 1 g four to six times daily,
- **Child 15-18 years:** 2 g twice daily (on rising and at bedtime) or 1 g four times daily (1 hour before meals and at bedtime) taken for 4-6 weeks (up to 12 weeks in resistant cases); maximum 8 g daily.

### Notes:

- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration
- Administer 1 hour before meals.
- Spread doses evenly throughout waking hours.
- *Bezoar formation:* Following reports of bezoar formation associated with sucralfate, the CSM has advised caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.
- Caution – absorption of aluminium from sucralfate may be significant in patients on dialysis or with renal impairment.
- Tablets may be crushed and dispersed in water.
- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by **at least 1 hour**. In rare cases bezoar formation has been reported when sucralfate suspension and enteral feeds have been given too closely together.
- Caution – sucralfate oral suspension may block fine-bore feeding tubes.
- Available as: oral suspension (1 g in 5 mL), tablets (1 g).

Evidence: [2, 6, 12]

## Temazepam

### Use:

- Sleep disturbance where anxiety is a cause.

### Dose and routes

#### By mouth,

- **Adult:** 10–20 mg at night. Dose may be increased to 40 mg at night in exceptional circumstances

### Notes:

- Not licensed for use in children.
- Oral solution may be administered via an enteral feeding tube.
- Available as: tablets (10 mg, 20 mg) and oral solution (10 mg/5 mL).
- Schedule 3 controlled drug

Evidence: [1, 12]

## Tizanidine

### Use:

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

### Dose and routes

#### Children doses based on SR [332]

- **Child 18 months – 7 years:** 1 mg/day; increase if necessary according to response,
- **Child 7 -12 years:** 2 mg/day; increase if necessary according to response,
- **Child >12 years:** as per adult dose [1]: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.

### Notes:

- Not licensed for use in children.
- Usually prescribed and titrated by neurologists.
- Timing and frequency of dosing is individual to the specific patient as maximal effect is seen after 2–3 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 and dry mouth are common side-effects.
- Tablets may be crushed and administered in water if preferred. May be administered via an enteral feeding tube - Tablets do not disperse readily, but will disintegrate if shaken in 10 mL of water for 5 minutes. The resulting dispersion will flush via an 8Fr NG tube without blockage.
- Available as: tablets (2 mg, 4 mg).

Evidence: [1, 12, 19, 20, 25, 332-335]

## 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 5-12 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum of 4 doses in 24 hours). Increase if necessary to a maximum dose of 3 mg/kg (maximum single dose 100 mg) every 6 hours,
- **Child 12-18 years:** initial dose of 50 mg every 4-6 hours. Increase if necessary to a maximum of 400 mg/day given in divided doses every 4-6 hours.

#### By IV injection or infusion

- **Child 5-12 years:** 1-2 mg/kg every 4-6 hours (maximum initial single dose of 50 mg; maximum 4 doses in 24 hours). Increase if necessary to a maximum dose of 3 mg/kg (maximum single dose 100mg) every 6 hours,
- **Child 12-18 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.
- Tramadol is a Schedule 3 CD but exempted from safe custody requirements.
- By mouth tramadol is about 1/10 as potent as morphine.
- Onset of action after an oral dose is 30 to 60 minutes. Duration of action is 4-9 hours.
- Causes less constipation and respiratory depression than the equivalent morphine dose.
- Analgesic effect is reduced by ondansetron.
- Soluble or orodispersible tablets may be dissolved in water for administration via an enteral feeding tube.
- Available as capsules (50 mg, 100 mg), soluble tablets (50 mg), orodispersible tablets (50 mg), m/r tablets and capsules (100 mg, 150 mg, 200 mg, 300 mg, 400 mg), oral drops (100mg/mL) and injection (50 mg/mL).

Evidence: [1, 2, 12, 29, 33]

## 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–18 years:** 15–25 mg/kg (maximum 1.5 g) 2–3 times daily.

##### *Menorrhagia*

- **Child 12-18 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 -18 years:** 10 mg/kg (maximum 1 g) 2-3 times a day.

By continuous intravenous infusion:

##### *Inhibition of fibrinolysis*

- **Child 1 month -18 years:** 45 mg/kg over 24 hours.

##### *Mouthwash 5% solution:*

- **Child 6-18 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.
- Parenteral preparation can be used topically.
- Available as: tablets (500 mg), syrup (500 mg/5mL available from 'specials' manufacturers) and injection (100 mg/mL 5 mL ampoules). Mouthwash only as extemporaneous preparation.

Evidence: [2, 6, 336-340]



## Trihexyphenidyl

### Uses:

- Dystonias; Sialorrhoea (drooling); Antispasmodic.

### Dose and route:

#### Oral

- **Child 3 months -18 years:** initial dose of 1-2mg daily in 1-2 divided doses, increased every 3-7 days by 1mg daily; adjusted according to response and side-effects; maximum 2mg/kg/daily (maximum 70mg/daily).

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

### Notes:

- Anticholinergic agent thought to act through partially blocking central (striatal) cholinergic receptors.
- Not licensed for use in children.
- Use in conjunction with careful observation and a full non-drug management programme including positioning, massage, holding, distraction, checking for causes of exacerbations etc. Advisable to seek specialist neurological input before use of trihexyphenidyl.
- Side-effects are very common and it is important to start at a low dose and increase gradually to minimise the incidence and severity. Mouth dryness, GI disturbance, blurring of vision, dizziness and nausea can occur in 30-50% patients. Less common side-effects include urinary retention, tachycardia and with very high doses CNS disturbance.
- Use with caution in children with renal or hepatic impairment.
- Onset of action is usually within 1 hour, maximum effect occurs within 2-3 hours and duration of effect ~6-12 hours.
- May take several weeks for maximal effect on dystonic movements to be seen.
- Do not withdraw abruptly in children who have been on long-term treatment.
- Tablets may be crushed and mixed in soft food.
- For administration via a gastrostomy the liquid may be used or the tablets will disperse readily in water.
- Available as: tablets 2mg and 5mg; oral liquid (pink syrup) 5mg in 5ml.

Reference: [1, 2, 12, 341-347]

## 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–18 year:** 250-300 micrograms/kg (maximum 10 mg) as a single dose.

### Notes:

- Caution with intravenous use in premature infants <2.5 kg.
- Available as Konakion MM injection 10 mg/mL (1 mL amp) for slow intravenous injection or intravenous infusion in glucose 5%; NOT for intramuscular injection.
- Available as Konakion MM Paediatric 10 mg/mL (0.2 mL amp) for oral administration or intramuscular injection. Also for slow intravenous injection or intravenous infusion in glucose 5%.
- There is not a UK licensed formulation of Vitamin K tablets currently available. Possible to obtain 10 mg phytomenadione tablets via a specialist importation company.

Evidence:[1-3, 6]

## Appendix 1: Morphine equivalence single dose [1, 2, 5]

Analgesic	Dose
Morphine oral	10mg
Morphine subcutaneous / intravenous	5mg
Diamorphine subcutaneous / intravenous	3mg
Hydromorphone oral	2mg
Oxycodone oral	6.7mg
Methadone	Variable

## Appendix 2: Subcutaneous infusion drug compatibility

Evidence suggests that in during end of life care in children, where the enteral route is no longer available, the majority of symptoms can be controlled by a combination of six “essential drugs” [348]. Compatibility for these six drugs is given in the table 1 below [5]. For more detailed information professionals are advised to consult an appropriate reference source [349]

**Table 1: Syringe driver compatibility for two drugs in water for injection**

Diamorphine							
-	Morphine sulphate						
-	-	Oxycodone					
+	+	+	Midazolam				
A	+	A	+	Cyclizine			
A	+	+	+	+	Haloperidol		
+	+	+	+	-	-	Levomepromazine	
+	+	+	+	+	+	+	Hyoscine hydrobromide

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

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