The Association of Paediatric Palliative Medicine Master Formulary

5th edition

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Foreword

It gives me great pleasure that we welcome the 5th edition of the APPM Master Formulary released on the 10th anniversary of the formation of the Association of Paediatric Palliative Medicine. The Formulary has become an important core resource for the prescriber working in paediatric palliative medicine.

The Formulary brings together all available paediatric palliative prescribing information in a single volume, utilising up to date published research and consensus expert opinion. It continues to keep pace with new guidance on existing medication and introduces newer drugs pertinent to the field of paediatric palliative medicine.
In this edition, we welcome an increase in our pharmacy support, a neonatologist and an international contingent of reviewers. Their engagement ensures the Formulary continually raises the quality standard and maintains clinical relevance. It is a reflection of the Formulary's success and impact that is now translated into several languages including Russian, Bahasa Indonesian and Spanish.

The ethos of maintaining a formulary that is free to access and download will continue via the APPM website (www.appm.org.uk). It is anticipated that revisions to the Formulary will now be every few years and a print format will be available to buy at cost via the APPM website.

The APPM wishes to acknowledge the meticulous, diligent work of Dr Sat Jassal for coordinating, leading and editing all Formulary editions to date. We are very grateful for the excellent pharmacy support, led by Anita Aindow and to the many contributors and reviewers, old and new, for their hard work and analytical eye. In particular we wish to thank our international colleagues for their input, whose insights and perspectives have been highly valuable. Finally thank you to the APPM membership for their peer review (and proof reading!) of the Formulary.

As with all previous editions, the Association of Paediatric Palliative Medicine is pleased to support the new 5th edition APPM Master Formulary as a clinically relevant and up to date publication, providing support to all prescribers caring for infants, children and young people requiring palliative care.

Dr Anna-Karenia Anderson (chair@appm.org.uk)
Chair of the Association for Paediatric Palliative Medicine

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Introduction

Welcome to the fifthedition of the APPM Master Formulary. Even in the short time since the publications of the 4th edition, there have been some major changes in the use of certain medications. The advice on many of the drugs monographs has been extensively rewritten and references have been brought up to date. New drugs have been added and additional indications have been inserted for many drugs. Following feedback we have added alot of new information on neonatal dosages and management.

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 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 in the UK and Ireland.

For each individual drug, evidence is cited from research papers (where available) on its usage. We have also cited the source(s) used to inform recommended drug dosages. 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 ideal we have been mindful of the fact that research into drug usage in babies and children and specifically in the area of palliative care is difficult, and as yet is 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 the United Kingdom. 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.

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

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 chair@appm.org.uk

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

This formulary is provided free of charge and all the contributors work to improve paediatric palliative care around the world. Feel free to make as many copies as you like but please do not alter, plagiarise or try to copy any of the work into your own name. If you wish to use the work in a specific way then contact us for approval by e-mailing chair@appm.org.uk

Abbreviations

SRE= strong research evidence

WRE= some weak research evidence

NoRE= no published evidence but has clinical consensus

ARE= evidence (research or clinical consensus) with adults

SC = subcutaneous

IV = intravenous

IM= intramuscular

CSCI = continuous subcutaneous infusion

CorGA = corrected gestational age

In general (and when available), this Formulary includes, for palliative care, the same doses as those recommended in one or more of: British National Formulary (BNF)[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 2019, but the dosages, indications, contraindications and adverse effects of drugs change over time as new information is obtained. It is the responsibility of the prescriber to check this information with the manufacturer's current data sheet and we strongly urge the reader to do this before administering any of the drugs in this document. In addition, palliative care uses a number of drugs for indications or by routes that are not licensed by the manufacturer. In the UK such unlicensed use is allowed, but at the discretion and with the responsibility of the prescriber.

Formulary

Acetazolamide

Use:

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

Dose and route:
Epilepsy

By mouth or slow intravenous injection:

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

Raised Intracranial Pressure

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

Notes:

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

Evidence: [1, 2, 5, 7-11] NoRE

Adrenaline (topical) (also known as Epinephrine)

Use:

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

Dose and routes:

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

For upper airway obstruction: By inhalation of nebulised solution

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

Evidence: [1-3, 5] NoRE

Alfentanil

Use:

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

Dose and Routes:

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

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

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

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

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

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

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

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

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

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

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

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

SC / Sublingual / Buccal

Suggest 10-16% of the total CSCI dose. However there is a very poor relationship between the effective PRN dose and the regular background dose, so start with low dose and titrate. Alfentanil has a quick onset of action (within 5 minutes after subcutaneous bolus injection),

but short duration of action (under 60 minutes). Even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Dose and frequency of administration should be regularly reviewed.

4. Procedure-related pain SEEK SPECIALIST ADVICE

SC / Sublingual / Buccal

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

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

Notes:

- Licensing: Alfentanil injection is licensed for use in children as an analgesic supplement for use before and during anaesthesia. Use for pain relief in palliative care is unlicensed. Buccal, sublingual or intranasal administration of alfentanil for incident/breakthrough pain is an unlicensed indication and route of administration.
- Useful for incident and breakthrough pain as faster onset, shorter acting, smaller volumes required compared with fentanyl.Dose required for breakthrough pain does not correlate with background analgesia requirement.
- There is limited information / evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.
- Potency: 10-20 times stronger than parenteral morphine, approximately 25% of the potency of fentanyl.
- Very useful in patients with severe renal failure (no dose reduction is needed). May need to reduce the dose 30-50% in severe hepatic impairment.
- 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 in patients from 1 month to 12 years of age, so higher infusion doses may be needed.
- Contraindication: not to be administered concurrently with MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Interaction: alfentanil levels are increased by inhibitors of Cytochrome P450.
- Adverse effects include respiratory depression, hypotension, hypothermia, muscle rigidity (which can be managed with neuromuscular blocking drugs).
- Metabolised by CYP3A4 and CYP3A5, so note potential interactions (including midazolam).
- For SC or IV infusion, alfentanil is compatible with 0.9% NaCl or 5% glucose as a diluent. For CSCI alfentanil appears physically compatible with most drugs used in a syringe driver. There is evidence for compatibility with midazolam. Note possible concentration-dependent incompatability with cyclizine: use water for injection as diluent and observe for crystallisation. Like diamorphine, high doses of alfentanil may be dissolved in small volumes of diluent which is very useful for SC administration.
- Available as: injection (500 microgram/mL in 2 ml and 10 ml ampoule); Intensive care injection (5 mg/mL in 1ml ampoule which must be diluted before use). Nasal spray with attachment for buccal / SL use (5 mg/5 mL bottle available as special order from

Torbay Hospital Manufacturing Unit Tel: 01803 664707. Each ‘spray’ delivers 0.14 ml = 140 microgram alfentanil. More costly than using injection preparation).

- Schedule 2 CD

Evidence: [1, 2, 5, 6, 12-15]
ARE, SRE (for PICU settings), NoRE (in palliative care settings outside ICU)

Amitriptyline

Use:

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

Dose and routes:
By mouth:

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

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

Notes:

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

Evidence: [1, 2, 5, 10, 16-20]

Aprepitant

Use:

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

Dose and route:
For oral administration:

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

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

Notes:

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

Evidence: [1, 5, 21-26]

Arachis Oil Enema

Use:

- Faecal softener
- Faecal impaction

Dose and route:
By rectal administration

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

Notes:

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

Evidence: [1, 2, 5, 6] NoRE

Atropine

Use:

- Reductionof death rattle
- Hypersalivation / Hypersecretion

Dose and route:
By sublingual administration

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

Notes:

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

Evidence: [1, 27-34] WRE

Baclofen

Use:

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

Dose and routes:
By mouth:

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

By Intrathecal injection:

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

Notes:

- Review treatment for spasticity if no benefit within 6 weeks of achieving maximum dose, and withdraw over 1-2 weeks if ineffective.
- Patient information: See Medicines for Children leaflet 'Baclofen for muscle spasm': www.medicinesforchildren.org.uk/baclofen-muscle-spasm
- Dependence and tolerance are unlikely, so preferable to diazepam.
- Likely onset of action for hiccups 4-8 hours, for muscle spasm in 1-2 days, for spasticity 3-4 days.
- For severe intractablehiccups –lower dose range to be used. May have direct effect on diaphragm.
- Balance efficacy against unwarranted additional effects of baclofen.
- There is very limited clinical data on the use of baclofen in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.
- Administer after food to reduce risk of gastric irritation.
- Monitor and review reduction in muscle tone and potential adverse effects on swallow, airway protection, posture and function. Drowsiness and nausea are common side effects.
- Impact of undesirable hypotonia may be minimised by reducing daytime and increasing evening doses.
- Intrathecal use may be considered, by specialist only, for severe chronic spasticity, if enteral treatment does not achieve control, is poorly tolerated, or higher doses are required.
- Avoid abrupt withdrawal as can precipitate serious psychiatric reactions and (especially after intrathecal use), life-threatening withdrawal syndrome including hyperactivity, increased spasticity, autonomic dysfunction. See PCF6 for management of this.
- Baclofen CSCI (using intrathecal preparation) may be used short term (after a test dose) to avoid sudden withdrawal when enteral and/or intrathecal routes become impossible.
- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.
- Contraindicated if there is a history of active peptic ulceration.
- Administration with or after food may minimise gastrointestinal irritation side effects.
- Peak plasma concentration achieved 0.5-1.5 hours after oral dose (site of absorption not documented).

- May be administered via enteral feeding tubes including gastrostomy or jejunostomy. (Specific data only available for some makes of liquid and tablet). Use liquid formulation for small doses; dilute prior to use to reduce viscosity. Consider dispersing tablets in water for higher doses owing to the sorbitol content of the liquid formulation. (Teva brand tablets produce a fine dispersion in 10 ml water).
- Available as: tablets (10 mg) and oral solution (5 mg/5 mL). Also intrathecal solution for infusion, for specialist 500 microgram/ml and 2 mg/ml.

Evidence: [1, 2, 5, 10, 35-44]

Bethanechol

Use:

- Opioid induced urinary retention

Dose and routes:
By mouth:

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

Subcutaneous:

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

Notes

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

Evidence: [1, 10, 45, 46]

Bisacodyl

Use:

- Constipation

Dose and routes:
By mouth:

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

By rectum (suppository):

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

Notes:

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

Evidence: [1, 2, 47]

Buprenorphine

Use:

- Moderate to severe pain

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

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

By CSCI

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

By transdermal patch:

- By titration or as indicated by existing opioid needs.

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

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

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

Notes:

- Sublingual tablets not licensed for use in children < 6 years old.
- Patches not licensed for use in children.
- Patches may cause contact allergies. Pre-treatment topically with budenoside inhalation spray to the area the patch is applied to may help.
- Causes less constipation than some other opioids.
- Athough no actual published evidence, in theory has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Not fully reversible with naloxone at least not with the regular dose since the binding capacity is so high you have to use much higher doses than regularly used.
- Sublingual duration of action 6-8 hours.
- Caution with hepatic impairment and potential interaction with many drugs including anti-retrovirals.
- Available as: tablets (200 microgram, 400 microgram) for sublingual administration. Tablets may be halved.

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

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

For patches, systemic analgesic concentrations are generally reached within 12–24 hours but levels continue to rise for 32–54 hours (pharmacokinetic profile may differ slightly between preparations, check SPC for full details).
If converting from:

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

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

Evidence: [1, 2, 5, 48-62]

Carbamazepine

Use:

- Neuropathic pain
- Some movement disorders
- Anticonvulsant

Dose and routes
By mouth:

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

By rectum:

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

Notes:

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

Evidence: [2, 10, 63-68]

Celecoxib

Use:

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

Dose and routes
By mouth:

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

Notes

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

Evidence: [1, 69-76] WRE

Chloral hydrate

Use:

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

Dose and routes:
By mouth or rectum:

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

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

Notes:

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

Evidence: [2, 3, 6, 77-87]

Chlorpromazine

Use:

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

Dose and routes:

Hiccups
By mouth:

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

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

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

By deep intramuscular injection:

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

Notes:

- Not licensed in children for intractable hiccup.
- Caution in children with hepatic impairment (can precipitate coma), renal impairment (start with small dose; increased cerebral sensitivity), cardiovascular disease, epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis.
- Caution is also required in severe respiratory disease and in children with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops).
- Photosensitisation may occur with higher dosages; children should avoid direct sunlight.
- Antipsychotic drugs may be contra-indicated in CNS depression.
- Risk of contact sensitisation; tablets should not be crushed and solution should be handled with care.
- Oral solution may be administered via an enteral feeding tube.There is no specific data relating to the jejunal administration of chlorpromazine. Monitor for loss of efficacy or increased side-effects.
- Available as: tablets, coated (25 mg, 50 mg, 100 mg); oral solution (25 mg/5 mL, 100 mg/5 ml ; injection (25 mg/mL and 2 mL ampoules).
- Over 16 years may have 100 mg base rectally. For equivalent therapeutic effect 100 mg chlorpromazine base given *rectally* as a suppository ≡
- 20–25 mg chlorpromazine hydrochloride *by intramuscular injection* ≡
- 40–50 mg of chlorpromazine base or hydrochloride given *by mouth*.But rectal administration is unlicensed use.

- Suppositories from specials manufacturers.

Evidence: [1, 2, 88-97]

Clobazam

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

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

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

Evidence: [2, 6, 98-100]

Clonazepam

Use:

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

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

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

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

For status epilepticus: (SR)

Continuous subcutaneousinfusion:

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

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

- **Neonate:** 100 micrograms/kg intravenous over at least 2 minutes, repeated after 24 hours if necessary (avoid unless no safer alternative). Used for seizures not controlled with phenobarbital or phenytoin.
- **Child 1 month-11 years:** Loading dose 50 micrograms/kg (maximum 1 mg) by IV injection followed by IV infusion of 10 micrograms/kg/hour adjusted according to response; maximum 60 micrograms/kg/hour.

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

Notes

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

Evidence: [2, 3, 41, 65, 98, 101-106]

Clonidine

Uses:

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

Doses and routes:

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

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

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

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

IV infusion: Can also be used as CSCI

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

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

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

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

Spasticity / Movement Disorder:
Oral:

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

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

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

When using patch (for children over 10 kg)

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

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

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

Conversion of patients on IV or oral clonidine:

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

IV/Oral tapering doses:

- Apply patch on day 1.
- Day 1 give 100% of oral/IV dose
- Day 2 give 50% of oral/IV dose
- Day 3 give 25% oral/IV dose [107]
- Day 4 patient will only need patch

Notes

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

- Oral bioavailability 75-100%; generally 1:1 conversion IV:oral is suggested as a starting point (largely adult data. Note: it has been suggested that oral bioavailability may be lower in children [108]).
- Some reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4 micrograms/kg have been used.
- Onset of effect: oral 30-60 mins. Time to peak plasma concentration: oral 1.5-5 hours; epidural 20 minutes; transdermal 2 days.
- CSCI can be useful to maintain control of dystonia in difficult cases.
- Clonidine has been used successfully by SC injection and infusion – seek specialist advice.
- Oral solution may be administered via an enteral feeding tube. Alternatively, if the required dose is appropriate to the available tablet strengths, the tablets may be crushed and dispersed in water for administration via an enteral feeding tube. The 25 microgram tablets do not appear to disperse in water as readily as the 100 microgram tablets. IV solution may also be given via the enteral tube. There is no specific information for jejunal administration. Administer as above but observe for any loss of efficacy or increased side effects.
- Chronic conditions – for older children the use of transdermal patches may be considered when an effective oral dose has been established which is great enough to allow an approximate conversion (1:1) to the transdermal route.
- Available as:
  tablets 25 micrograms, 100 micrograms;
  injection150 micrograms/mL;
  transdermal patch
  2.5 mg (=100 micrograms clonidine/day for 7 days),
  5 mg (=200 micrograms clonidine/day for 7 days) or
  7.5 mg (= 300 micrograms clonidine/day for 7 days),
  (transdermal patches not licensed in UK – available via importation company); oral solution (special) 50 micrograms/mL.

Evidence: [3, 84, 108-130]

Co-danthramer (dantron and poloxamer 188)

Use:

- Constipation in terminal illness only

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

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

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

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

Notes

- Co-danthramer is made from dantron and poloxamer ‘188’.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- No longer used in adult palliative care patients due to excoriation of skin around anus.
- Dantron can turn urine red/brown.
- Suspension can be used with enteral feeding tubes but is quite viscous, needing some pressure on syringe and to be flushed well after administration. Administration into the jejunum is unlikely to affect pharmacological response.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [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 50 mg/ Docusate sodium 60 mg)

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

Notes

- Not recommended for under 6 years.
- Co-danthrusate is made from dantron and docusate sodium.
- Acts as a stimulant laxative.
- Avoid prolonged skin contact due to risk of irritation and excoriation(avoid in urinary or faecal incontinence, or children with nappies).
- Dantron can turn urine red/brown.
- No specific data on enteral tube administration are available for this preparation. If necessary use the suspension and flush tube well after use. Consider diluting with water to aid administration.
- Rodent studies indicate potential carcinogenic risk.

Evidence: [1, 2, 131]

Codeine Phosphate

Codeine is no longer indicated for palliative care in children. It has been replaced by other opioids, particularly oral morphine and buccal diamorphine or fentanyl.

Evidence: [1-3, 65, 132, 133]

Cyclizine

Use:

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

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

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

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

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

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

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

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

Notes:

- Antihistaminic antimuscarinic antiemetic.
- Tablets are not licensed for use in children < 6 years old.
- Injection is not licensed for use in children.
- Antimuscarinic side-effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Increased sedative effect when given with tricyclics, anxiolytics, MAOI's.
- Increased antimuscarinic effect when given with tricyclics, antimuscarinics, MAOI's
- Theoretically antagonises betahistine, histamine.
- Avoid in patients on midodrine and children with severe liver disease. In severe cardiac failure may cause fall in cardiac output. Increased risk of transient paralysis with intravenous use in patients with neuromuscular disorders.
- Rapid SC or IV bolus can lead to 'lightheadness' –disliked by some and enthralling to others leading to repeated requests for IV cyclizine.
- For CSCI or IV infusion, dilute only with water for injection or 5% dextrose;*incompatible*with 0.9 %NaCland will precipitate.
- Concentration dependent incompatibility with alfentanil, dexamethasone, diamorphine and oxycodone.
- Suppositories must be kept refrigerated.
- Tablets may be crushed for oral administration. The tablets do not disperse well in water, but if shaken in 10 mL water for 5 minutes, the resulting dispersion may be administered immediately via an enteral feeding tube. There is no specific information for jejunal administration. If this route is used monitor for any loss of efficacy or increased side-effects.
- Available as: tablets (50 mg), suppositories (12.5 mg, 25 mg, 50 mg, 100 mg from 'specials' manufacturers) and injection (50 mg/mL).

Evidence: [2, 10, 134-137]

Dantrolene

Use:

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

Dose and routes:

The dose of dantrolene should be built up slowly
By mouth:

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

Notes:

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

Evidence: [2, 36, 37, 42, 138, 139]

Dexamethasone

Use:

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

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

Dose and routes
Prescribe as dexamethasone base.

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

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

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

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

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

Evidence: [6, 95, 140-143]

Diamorphine

Use:

- Moderate to severe pain.
- Dyspnoea

Dose and routes:

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

By continuous subcutaneous or intravenous infusion

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

By IV /SC or IMinjection:

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

By intranasal or buccal route:

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

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

720 micrograms/actuation (Ayendi$^{(R)}$)

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

1600 micrograms/actuation (Ayendi$^{(R)}$)

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

Intermittent pain without background opioids

Buccal, IV or SC route
- 30 micrograms/kg 1–4 hrly as needed.

Breakthrough pain

By buccal, subcutaneous or IV routes

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

Dyspnoea

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

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

Evidence: [1, 2, 6, 65, 144-146]

Diazepam

Use:

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

Dose and routes

Short term anxiety relief, panic attacks and agitation

By mouth:

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

Relief of muscle spasm

By mouth:

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

Status epilepticus

By IV injection over 3–5minutes:

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

Child 1 month–11 years: 300-400 micrograms/kg (max 10 mg) repeated once after 10 minutes if necessary

Child 12–17 years: 10 mg repeated once after 10 minutes if necessary.

By rectum (rectal solution):

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

Notes

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

- Onset of action: apprx 15 minutes given orally and within 1-5 minutes given intravenously. Given as rectal solution, diazepam is rapidly absorbed from the rectal mucosa with maximum serum concentration reached within 17 minutes.
- Long plasma half-life of 24-48 hours. The active metabolite, nordiazepam, has a plasma half-life of 48-120 hours.
- The oral solution may be administered via a gastrostomy tube. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.
- Available as: tablets (2 mg, 5 mg, 10 mg), oral solution/suspension (2 mg/5 mL, 5 mg/5 mL), rectal tubes (2.5 mg, 5 mg, 10m g), and injection (5 mg/mL solution and 5 mg/mL emulsion).Schedule 4 (CD Benz).

Evidence: [1, 2, 6, 10, 36, 42, 102, 147-152]

Diclofenac Sodium

Use:

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

Dose and routes
By mouth or rectum:

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

By IV infusion:

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

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

- Not licensed for use in children under 1 year; *suppositories* not licensed for use in children under 6 years (except for use in children over 1 year for juvenile idiopathic arthritis); solid dose forms containing more than 25mg not licensed for use in children; injection(IV infusion only) not licensed for use in children.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use. However, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.
- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects: piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk).
- Use with caution in children with cardiac, hepatic or renal impairment and those with asthma.
- Smallest dose that can be given practically by rectal route is 3.125 mg by cutting a 12.5 mg suppository into quarters (CC).
- For IV infusion, dilute in 5% glucose or 0.9% NaCl (previously buffered with sodium bicarbonate) and infuse over 30-120 minutes.
- Dispersible tablets may be administered via an enteral feeding tube. Disperse immediately before administration. There should be no reduction in bioavailability from jejunal administration.
- Available as: gastro-resistant tablets (25 mg, 50 mg), modified-release tablets (25 mg, 50 mg, and 75 mg), modified release capsules (75 mg and 100 mg), injection (25 mg/mL Voltarol^{R} for IV infusion only), and suppositories (12.5 mg, 25 mg, 50 mg and 100mg).

Evidence: [2, 6, 10, 89]

Dihydrocodeine

Use:

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

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

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

Notes:

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

Evidence: [2, 5, 65, 89] ARE, NoRE for injection

Docusate

Use:

- Constipation (faecal softener).

Dose and routes
By mouth:

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

By rectum:

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

Notes:

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

Evidence: [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 use of domperidone in palliative care is excluded from these recommendations HOWEVER caution should be exercised nevertheless.

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

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

Use:

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

Dose and routes
For nausea and vomiting
By mouth:

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

For gastro-oesophageal reflux and gastrointestinal stasis
By mouth:

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

Notes

- Domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- Domperidone is contraindicated in those:
  - With conditions where cardiac conduction is, or could be, impaired
  - With underlying cardiac diseases such as congestive heart failure
  - Receiving other medications known to prolong QT interval(e.g. erythromycin, ketoconazole) or which are potent CYP3A4 inhibitors
  - With severe hepatic impairment
- This risk may be higher with daily doses greater than 30 mg. Use at lowest effective dose.

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

Evidence: [2, 3, 6, 10, 153-158]

Entonox (nitrous oxide)

Use:

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

Dose and routes
By inhalation:

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

Notes:

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

Evidence: [2, 159-161]

Erythromycin

Use:

- Gastrointestinal stasis (motilin receptor agonist).

Dose and routes
By mouth or by intravenous infusion:

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

Notes:

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

Evidence: [2, 162, 163] WRE

Etoricoxib

Uses:

- Anti-inflammatory analgesic; adjuvant for musculoskeletal pain

Dose and route:
Oral:

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

Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.
- Etoricoxib is not licensed for use in children less than 16 years of age. The pharmacokinetics of etoricoxib in children less than 12 years of age has not been studied.
- Etoricoxib may mask fever and other signs of inflammation.
- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID or in those with a coagulation disorder. However, etoricoxib may be better tolerated than other NSAIDs in patients with known hypersensitivity.
- Etoricoxib is contraindicated in those with: active peptic ulceration or active GI bleeding; severe hepatic or renal dysfunction; inflammatory bowel disease or congestive heart failure.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. All NSAIDs are associated with GI toxicity. In adults evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper GI side-effects with piroxicam and ketorolac associated with the highest risk and ibuprofen at low to medium dose with the lowest risk. Children appear to tolerate NSAIDs better than adults and GI side-effects are less common although they do still occur.
- Common adverse events (1-10% patients): alveolar osteitis; oedema/fluid retention; dizziness, headache; palpitations, arrhythmia; hypertension; bronchospasm; abdominal pain; constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer; ALT increased, AST increased; ecchymosis; asthenia/fatigue, flu-like disease.
- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Etoricoxib does NOT appear to inhibit or induce CYP isoenzymes. However, the main pathway of etoricoxib metabolism is dependent on CYP enzymes (primarily CYP3A4) so co-administration with drugs that are inducers or inhibitors of this pathway may affect the metabolism of etoricoxib.
- Etoricoxib tablets may be dispersed in 10ml water and will disintegrate to give fine granules that settle quickly but disperse easily and flush down an 8Fr NG or gastrostomy tube without blockage. There are no specific data relating to the jejunal administration of etoricoxib. Administer as above and monitor for lack of efficacy or increased side-effects.
- Available as: film coated tablets 30 mg, 60 mg, 90 mg, 120 mg. Tablets contain lactose.

Evidence: [1, 164, 165] SR EA

Fentanyl

Use:

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

Dose and routes
Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in the opioid naive patient. The maximum dose stated applies to **starting** dose only.

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

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

•not exceeding the prescribed dose;

• following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application;

•not cutting patches and avoiding exposure of patches to heat including via hot water;

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

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

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

By transdermal patch or continuous infusion:

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

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

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

By oromucosal application (lozenge with oromucosal applicator)

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

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

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

By continuous intravenous/subcutaneous infusion

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

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

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

Notes:

- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.
- In neonatology there is no lower CorGA as fentanyl is used for endotracheal intubation at all gestations.
- Can be safely used in poor, deteriorating or absent renal function.
- Avoid or reduce dose in hepatic impairment.
- Synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.
- Evidence that it is less constipating than morphine has not been confirmed in more recent studies[166].
- Consider reducing starting doses in obese children – to use ideal body weight rather than actual body weight.
- Fentanyl products for the treatment of breakthrough pain are not interchangeable. If patients are switched from another fentanyl containing product a new dose titration is required.
- For break through pain, fentanyl effect is idiosyncratic: start at significantly lower doses than the equivalent for oral morphine. Always start at lower doses then titrate up.

Intranasal

- Intranasal route works more quickly and is shorter lasting than oromucosal.
- Pharmacokinetics of fentanyl intranasally arefavourable but it isnot always practical and/or well tolerated in children.
- Intranasal route has also been used for management of respiratory distress in paediatric palliative care.
- Injection solution can be administered by the intranasal route for doses less than 50micrograms which is the lowest strength of nasal spray available.

- Injection solution can be administered drop wise via nasal route (may be unpleasant) or using an atomiser device such as that used by A+E units for intranasal diamorphine.

Lozenges

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

Fentanyl transdermal patches

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

Formulations

- Intranasal spray Instanyl^{R} (50 micrograms/metered spray, 100micrograms/metered spray and 200 micrograms/metered spray). PecFent^{R} (100 micrograms/metered spray and 400 micrograms/metered spray).
  Lozenge with oromucosal applicator Actiq^{R} (200 micrograms, 400 micrograms,600 micrograms, 800 micrograms, 1.2 mg and 1.6 mg).
  Sublingual/buccal tablets Abstral$^{(R}$ (100, 200, 300, 400, 600 and 800 micrograms) Recivit$^{®}$ (133, 267, 400 and 800 micrograms) and buccal tablets Effentora$^{(R)}$ (100, 200, 400, 600 and 800 micrograms); Breakyl$^{(R)}$ (200, 400, 600, 800 and 1200 micrograms).

Patches: various manufacturers (12 micrograms/hour, 25 micrograms/hour, 50 micrograms/hour, 75 micrograms/hour, 100 micrograms/hour); Ionys® transdermal system (40 microgram/dose)
Injection: 50 microgram per mL

- Schedule 2 CD

Evidence: [2, 4, 5, 13, 144, 167-190]

Fluconazole

Use:

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

Dose and routes

Mucosal candidal infection

By mouth or intravenous infusion:

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

Invasive candidal infections and cryptococcal infections

By mouth or intravenous infusion:

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

Prevention of fungal infections in immunocompromised patients

By mouth or intravenous infusion

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

Notes:

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

Evidence: [2, 10, 191, 192]

Fluoxetine

Use:

- Major depression.

Dose and routes
By mouth:

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

Notes:

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

Evidence: [1, 2, 193-200]

Gabapentin

Important safety information

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

MHRA/CHM advice: Gabapentin (Neurontin®): risk of severe respiratory depression (October 2017)

Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, and concomitant use of central nervous system (CNS) depressants might be at higher risk of experiencing severe respiratory depression and dose adjustments may be necessary in these patients.

Use:

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

Dose and routes

Epilepsy
Consult BNFc or local neurology protocols

Neuropathic pain
By mouth:

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

Gabapentin to Pregabalin Switch for neuropathic pain
Consult appendix 3

Notes:

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

gabapentin. Administer using the above method. Monitor for loss of efficacy or increased side-effects.

- Available as: capsules (100 mg, 300 mg, 400 mg); tablets (600 mg, 800 mg), oral solution 250 mg/5 mL (Neurontin, United States import).
- Schedule 3 controlled drug but exempt from safe custody requirements.

Evidence: [1, 2, 10, 63, 65, 201-221] NoRE, WRE

Gaviscon®

Use:

- Gastro-oesophageal reflux, dyspepsia and heartburn.

Dose and routes
By mouth:

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

Gaviscon Liquid and Tablets

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

Gaviscon Advance

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

Notes:

- Gaviscon Infant Sachets licensed for infants and young children up to 2 years of age but use <1 year only under medical supervision. Gaviscon liquid and tablets are licensed for use from 2 years of age but age 2-6 years only on medical advice. Gaviscon Advance suspension and tablets are licensed for use from 12 years of age; use under 12 years on medical advice only.
- Gaviscon Infant should not to be used with feed thickeners, nor in patients with excessive fluid losses, (e.g. fever, diarrhoea, vomiting).
- Gaviscon Liquid contains 3.1 mmol sodium per 5mL; Gaviscon tablets contain 2.65 mmol sodium and also contain aspartame. Gaviscon Infant Sachets contain 0.92 mmol sodium per dose (half dual sachet).
- Available as: Gaviscon liquid and tablets; Gaviscon Advance suspension and tablets; Infant Sachets (comes as dual sachets, each half of dual sachet is considered one dose).
- Can be administed via nasogastric tube or gastrostomy. Not appropriate for administration via jejunostomy.

Evidence: [1-3]

Glycerol (glycerin)

Use:

- Constipation.

Dose and routes
By rectum:

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

Notes:

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

Evidence: [1, 2, 89] NoRE

Glycopyrronium bromide

Use:

- Control of upper airways secretion and hypersalivation.

Dose and routes
By mouth:

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

Subcutaneous / Intravenous injection:

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

Continuous subcutaneous / intravenous infusion:

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

Notes:

- Licensed oral solutions (Sialanar®K, Colonis Pharma generic) are licensed for use in children from 3 years of age with a chronic neurological disorder, for chronic pathological drooling. Not licensed for use in children for control of upper airways secretion and hypersalivation.
- Excessive secretions can cause distress to the child, but more often cause distress to those around him/her.
- Treatment is more effective if started before secretions become too much of a problem.
- Glycopyrronium does not cross the blood brain barrier and therefore has fewer side effects than hyoscine hydrobromide, which is also used for this purpose. Also fewer cardiac side effects.
- Slower onset response than with hyoscine hydrobromide or butylbromide.
- Oral absorption of glycopyrronium is very poor with wide inter-individual variation.
- Adult evidence for use in smooth muscle spasm (e.g. intestine, bladder), inoperable intestinal obstruction, para-neoplastic pyrexia and sweating and hyperhidrosis.
- Administration by CSCI: good compatibility data available for mixing with other commonly used palliative agents.
- Oral solution: Co-administration with food results in a marked decrease in systemic medicinal product exposure. Dosing should be at least one hour before or at least two hours after meals, or at consistent times with respect to food intake. High fat food should be avoided. Where the child's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake.
- For administration via an enteral feeding tube, tablets may be dispersed in water immediately prior to administration, or use the oral solution. Flush tube immediately with 10-20 mL water. There is no specific data on jejunal administration of

glycopyrronium. Administer using the above method. Monitor for loss of efficacy or increased side-effects.

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

Evidence: [2, 30, 206, 222, 223]

Haloperidol

Use:

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

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

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

By mouth for *restlessness and confusion*:

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

By mouth for *intractable hiccups:*

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

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

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

Notes:

- D2 receptor antagonist and typical antipsychotic.
- For dosage in psychosis please discuss with child psychiatrist.
- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for IM administration in adults; IV and SC administration off-label (all ages).
- Haloperidol can cause potentially fatal prolongation of the QT interval and Torsades de Pointes, particularly if given IV (off-label route) or at higher than recommended doses. Caution is required if any formulation of haloperidol is given to patients with an underlying predisposition e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT interval. If IV haloperidol is essential, ECG monitoring during drug administration is recommended.
- Side effects vary between age groups, with behavioural problems being common in children.
- Dosages for restlessness and confusion are often higher.
- Adult dosages can exceed 15 mg/24 hours in severe agitation.

- Oral doses are based on an oral bioavailability of ~50% of the parenteral route i.e. oral doses ~2x parenteral.
- Useful as long acting: – once daily dosing is often adequate.
- Oral solutions may be administered via NG tube or gastrostomy without further dilution. Flush tube well following administration. There is no specific data relating to jejunal administration of haloperidol. Administer using the above method. Monitor for increased side-effects or loss of efficacy.
- Available as: tablets (500 micrograms, 1.5 mg, 5 mg, 10 mg), capsules (500 micrograms), oral liquid (200 micrograms/mL, 1 mg/mL, 2 mg/mL), and injection (5 mg/mL).

Evidence: [1, 2, 5, 6, 10, 142, 224-233]

Hydromorphone

Use:

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

Dose and routes
Normally convert using oral morphine equivalent (OME) from previous analgesia.
Use the following **starting** doses in opioid naive patient. The maximum dose stated applies to **starting** dose only.

By mouth:

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

By IV or SC injection:

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

Notes:

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

Evidence: [1, 2, 4, 5, 48, 65, 171, 172, 234-239] No RE, ARE

Hyoscine butylbromide

Use:

- Adjuvant where pain is caused by spasm of the gastrointestinal or genitourinary tract (smooth muscle spasm)
- Antisecretory effect in bowel obstruction
- Management of secretions, especially where drug crossing the blood brain barrier is an issue
- Management of noisy breathing at the end of life (may be more effective if started early)

Dose and routes
By mouthor IM or IV injection:

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

By continuous subcutaneous infusion:

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

Notes:

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

Evidence: [1, 2, 10, 30, 223, 240-245]

Hyoscine hydrobromide

Use:

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

Dose and routes
By mouth or sublingual:

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

By transdermal route:

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

By SC or IV injection or infusion:

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

Notes:

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

Evidence: [1, 2, 30, 89, 222, 223, 243]

Ibuprofen

Use:

- Simple analgesic
- Pyrexia
- Adjuvant for musculoskeletal pain.

Dose and routes
By mouth:

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

Pain and Inflammation (by mouth using modified release preparation)

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

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

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

In systemic juvenile idiopathic arthritis:

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

Notes:

- **Will cause closure of ductus arteriosus; contraindicated in duct dependent congenital heart disease.**
- Orphan drug licence for closure of ductus arteriosus in preterm neonate.
- Not licensed for use in children less than 3 months of age or weight less than 5kg, except for up to two doses for post immunisation pyrexia. (50mg/dose given a minimum of 6 hours apart).
- Topical preparations and granules are not licensed for use in children.
- Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.
- Ibuprofen is a non-opioid analgesic, NSAID and non-selective COX inhibitor.
- Its analgesic effect can be as potent as low dose morphine.
- The risk of cardiovascular events secondary to NSAID use is undetermined in children. In adults, all NSAID use (including cyclo-oxygenase-2 selective inhibitors)

can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those patients receiving high doses long term. A small increased thrombotic risk cannot be excluded in children.

- All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects—piroxicam and ketorolac are associated with the highest risk; indometacin, diclofenac, and naproxen are associated with intermediate risk, and ibuprofen with the lowest risk (although high doses of ibuprofen have been associated with intermediate risk).
- Caution in asthma and during chemotherapy, and look out for symptoms and signs of gastritis.
- Consider use of a proton pump inhibitor with prolonged use of ibuprofen.
- For administration via an enteral feeding tube, use a liquid preparation; dilute with an equal volume of water immediately prior to administration where possible. No specific information for jejunal administration. Administer as above and monitor for any signs of loss of efficacy or increased side-effects.
- Ibuprofen can be used topically particularly for sprains, strains and arthritis.
- Available as: tablets (200 mg, 400 mg, 600 mg), modified release tablet (800 mg), orodispersible tablets (200 mg), chewable capsules (100 mg), capsules (200 mg, 400 mg), modified release capsules (200 mg, 300 mg), oral syrup (100 mg/5 mL), granules (600 mg/sachet), and spray, foam (50 mg per 1 g) creams and gels (5%).

Evidence: [1-3, 10, 246-250]

Ipratropium Bromide

Use:

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

Dose and routes:
Nebulised solution

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

Aerosol inhalation

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

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

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

Notes

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

Evidence: [2, 6, 251, 252] SRE

Ketamine

Use:

- Adjuvant to a strong opioid for neuropathic pain.
- Severe visceral pain / visceral hyeralgesia[5].
- Ischaemic pain.
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance.
- Emerging use in refractory status epilepticus.
- In neonates: for induction and maintenance of anaesthesia during procedures.
- Psychiatric use for treatment resistant depression in adolescents (secondary effect that this may offer, rather than because we advocate starting drugs for psychiatric diagnoses).

Dose and routes
By mouth or buccal or sublingual:

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

By continuous SC or IV infusion:

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

By intravenous administration*for anaesthesia*.

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

Notes:

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

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

Evidence: [2, 172, 237, 253-272] WRE, ARE

Ketorolac

Use:

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

Doses and routes:

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

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

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

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

Sublingual

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

SC bolus

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

CSCI

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

Notes:

- Ketorolac is a non-opioid, NSAID and preferential COX-1 inhibitor which has potent analgesic effects with only moderate anti-inflammatory action.
- Licensed only for the short-term management (maximum of 2 days) of moderate to severe acute postoperative pain in adults and adolescents from 16 years of age.
- SC administration is an unlicensed route of administration.
- Contraindications: previous hypersensitivity to ketorolac or other NSAIDs; history of asthma; active peptic ulcer or history of GI bleeding; severe heart, hepatic or renal failure; suspected or confirmed cerebrovascular bleeding or coagulation disorders. Do not use in combination with any other NSAID.
- Dose in adults with mild renal impairment should not exceed 60mg/day.
- All NSAIDs are associated with GI toxicity. In adults, evidence on the relative safety of NSAIDs indicates ketorolac and piroxicam are associated with the highest risk. Use the lowest effective dose for the shortest time. In addition, consider use in combination with a gastro-protective drug especially if ketorolac is used for a prolonged period (outside the licensed indication). Use of ketorolac in adults carries a 15 times increased risk of upper gastrointestinal complications, and a 3 times increased risk compared with other nonselective NSAIDs.
- In adults all NSAID use can, to varying degrees, be associated with a small increased risk of thrombotic effects. The risk of cardiovascular effects secondary to NSAID use is undetermined in children, but in adults, ketorolac is associated with the highest myocardial infarction risk of all NSAIDs.

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

Evidence: [1, 237, 273-285]

Lactulose

Use:

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

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

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

Hepatic encephalopathy:

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

Notes:

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

Evidence: [1, 2, 5, 6, 89, 286-290]

Lansoprazole

Uses:

- Gastro-oesophageal reflux disease; erosive oesophagitis; prevention and treatment of NSAID induced gastric and oesophageal irritation; treatment of duodenal and gastric ulcer.
- Fat malabsorption despite pancreatic enzyme therapy in cystic fibrosis

Dose and routes:
Oral

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

Notes:

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

can be swallowed whole with water or mixed with a small amount of water if preferred. FasTabs contain lactose and aspartame and should be used with caution in known PKU patients.

- For administration via a NG or gastrostomy tube, lansoprazole FasTabs can be dispersed in 10 mL water and administered via an 8Fr NG tube without blockage. For smaller bore tubes, dissolve the contents of a lansoprazole capsule in 8.4% sodium bicarbonate before administration. If the tube becomes blocked, use sodium bicarbonate to dissolve any enteric coated granules lodged in the tube. Lansoprazole less likely than omeprazole MUPS to cause blockage of small bore tubes.Lansoprazole is absorbed in the small bowel; therefore, jejunal administration is not expected to reduce bioavailability. Administer as above.
- Available as 15 mg and 30 mg capsules and 15 mg and 30 mg orodispersible tablets.

Evidence: [1, 2, 5, 10, 291-305]

Levetiracetam

Use:

- Epileptic seizures

Dose and route:

Background seizure management

By mouth.

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

By intravenous route

- **Body weight up to 50 kg:**10 mg/kg once daily then increase in steps of up to 10mg/kg twice daily (maximum per dose 30mg/kg twice daily). Dose to be increased every 2 weeks
- **Body weight 50 kg and above:** 250 mg twice daily then increase in steps of 500 mg twice daily (maximum per dose 1.5 g twice daily). Dose to be increased every 2-4 weeks

By Continuous Subcutaneous or Intravenous Infusion.

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

Management of breakthrough seizures

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

No need to measure levels

By enteral, subcutaneous or intravenous route

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

Notes:

- Benefits of levetiracetam over phenobarbitone or phenytoin for breakthrough seizure management include fewer side effects and lower volume enteral dose availability.
- Can be combined in syringe driver with midazolam, morphine, hyoscine butylbromide, hydromorphone, methotrimeprazine, metoclopramide, dexamethasone, haloperidol, glycopyrrolate and clonidine.

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

Evidence: [1, 2, 306-309] NoRE

Levomepromazine

Use

- Broad spectrum antiemetic where cause is unclear, or where probably multifactorial.
- Second line if a specific antiemetic fails.
- Antipsychotic and anxiolytic
- Sedation for terminal agitation

Dose and routes
Used as antiemetic
By mouth:

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

By continuous IV or SC infusion over 24hours:

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

By SC or IV injection:

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

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

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

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

Notes:

- Licensed for use in children with terminal illness for the relief of pain and accompanying anxiety and distress.
- A low dose is often effective as antiemetic. Titrate up as necessary. Higher doses are very sedative and this may limit dose increases.
- If the child is not stable on high dosage for nausea and vomiting, reconsider cause and combine with other agents e.g. dexamethasone.
- Some experience in adults withbuccal use at low dose as antiemetic (e.g. 1.5 mg three times daily as needed).
- Can cause hypotension, particularly with higher doses. Somnolence and asthenia are frequent side effects.
- Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of cytochrome P450 2D6. Co-administration of levomepromazine and drugs

primarily metabolised by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of these drugs.
- May lower seizure threshold.
- Avoid, or use with caution, in patients with liver dysfunction or cardiac disease. Start at low dose in patients with severe renal impairment and give once daily, titrating according to response.
- Tablets may be halved or quartered to obtain smaller doses. Tablets/segments may be dispersed in water for administration via a NG or gastrostomy tube. Flush tube well after administration.There is no specific information relating to jejunal administration of levomepromazine. Administer using the above method. Monitor for loss of efficacy or increased side-effects.
- For SC infusion dilute with sodium chloride 0.9%. Water for injection may also be used. The SC dose is considered to be twice as potent as that administered orally.
- Available as: tablets (25 mg) and injection (25 mg/mL). A 6 mg tablet is also available via specialist importation companies. An extemporaneous oral solution may be prepared.

Evidence: [1, 2, 5, 10, 310-313] CC, EA

Lidocaine (Lignocaine) patch

Use

- Localised neuropathic pain

Dose and routes
Topical:

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

Notes:

- Not licensed for use in children or adolescents under 18 years.
- The lidocaine in the plaster diffuses continuously into the skin, providing a local analgesic effect. The mechanism by which this occurs is through stabilisation of neuronal membranes, thought to cause down-regulation of sodium channels resulting in pain reduction.
- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes.
- When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 hours) about 3± 2% of the total applied lidocaine dose is systemically available and is similar for single and multiple administrations.
- Maximum recommended number of patches in adults currently is 3 per application.
- The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product.
- The plaster should be used with caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.
- An adequate treatment period is a minimum of 4 weeks in duration. Consider discontinuation if no response.
- For long-term use, treatment should be reviewed regularly to assess whether the number of plasters required can be reduced or the plaster-free period extended.
- The plasters must be used within 14 days of opening the sachets.
- A recent analysis by anatomic site of patch placement suggests that application to the head was tolerated less well compared with the trunk and extremities.
- Doses extrapolated from BNF on line Aug 2019.
- Available as 700 mg/medicated plaster (5% w/v lidocaine).

Evidence: [1, 5, 314-321] NoRE, ARE

Lomotil® (co-phenotrope)

Use:

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

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

By mouth:

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

Notes:

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

Evidence: [1, 2, 322-325]

Loperamide

Use:

- Diarrhoea from non-infectious cause
- Faecal incontinence
- Management of high ileostomy output

Dose and routes for management of chronic diarrhoea
By mouth:

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

Notes:

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

Evidence: [1, 2, 10, 326-328]

Lorazepam

Use

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

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

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

Sublingual:

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

For status epilepticus
By Slow IV injection:

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

Notes

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

Evidence: [2, 5, 10, 225, 329] NoRE, ARE

Macrogols

Use

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

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

By mouth for constipation or prevention of faecal impaction:

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

By mouth for faecal impaction:

- **Child under 1 year:** ½-1 paediatric sachet daily
- **Child 1–4 years:** 2 paediatric sachets on first day and increase by 2 sachets every 2 days (maximum 8 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy
- **Child 5–11 years:** 4 paediatric sachets on first day and increase by 2 sachets every 2 days (maximum 12 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy
- **Child 12–17 years:** 4 sachets daily of **adult** preparation, then increase by 2 sachets daily to a maximum of 8 adult sachets daily. Total daily dose should be drunk within a 6 hour period. After disimpaction switch to maintenance laxative therapy.

Notes

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

Evidence: [1, 2, 10, 287, 330, 331]

Melatonin

Use:

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

Dose and routes
By mouth:

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

Notes:

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

Evidence: [1, 2, 332-349] NoRE

Methadone

(WARNING: requires specialist advice)

Use:

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

Caution:

Methadone should only be commenced by practitioners experienced in its use.
This is due to wide inter-individual variation in response, very variable conversion ratios with other opioids, complex pharmacokinetics and a long half life.
Initial close monitoring is particularly important.

Dose and routes

In opioid naïve children

By mouth:

- **Child 1-12 years:** 30-100 micrograms/kg (maximum 5mg/dose initially) 1-3 times daily
- **Child >12 years:**100-200 micrograms/kg every 8-12 hours (maximum 5 mg/dose initially)
- Methadone has a long and variable half-life with potential to cause sedation, respiratory depression and even death from secondary peak phenomenon.
- Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may berequired for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose may be sufficient. To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 25% approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently).
- Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.
- For breakthrough pain, we would recommend using a short half-life opioid.

In opioid substitution/ rotation or switch

Caution:

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

- It can be difficult to convert a short or long acting opioid to an equivalent dose of methadone. Current practice is usually to admit to a specialist inpatient unit for 5-6 days or titrate orally at home with **very close** supervision.
- Other opioids should be considered first, if switching from morphine due to unacceptable effects or inadequate analgesia.

Consultation with a pain clinic or specialist palliativecare service is advised

Equianalgesic doses:

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

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

Ref [4]

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

- One approach incorporates a transition period where the dose of the former opioid is reduced and partially replaced by methadone which is then titrated upwards [350]. This approach is considered safer.

- In another approach, previous opioid therapy is completely stopped before starting a fixed dose of methadone at variable dose intervals [351]. This approach carries more risks.

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

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

Conversion rate: (Morphine in mg: Methadone in mg)
OME 30-90 mg/day = 4:1[352]
OME 90-300 mg/day = 6:1[352]
OME 301-600 mg/day = 8:1[352]
OME 601-800 mg/day = 12:1 [353]
OME 801-1000 mg/day = 15:1[353]

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

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

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

To make a complete switch to methadone

1. Calculate the total oral morphine requirement (or oral morphine equivalent (OME), if using a different opioid) over the previous 48 hours and calculate the average 24 hour requirement. Do not include breakthrough doses for incident pain. When calculating OME always use the lowest conversion dose.
2. Reduce the total oral daily dose OME by 30-50% to account for incomplete cross tolerance.
3. Convert the final calculated oral morphine daily dose to oral methadone daily dose by dividing by 15 (most guides say 10 so this is a cautious approach).
4. Divide this into three daily doses. (As a rule, the initial dose should not usually exceed 10 mg 3x per day in an adult/patient over 50 kg, 5 mg 3x per day in child/patient under 50 kg). Initially give either 2 or 3 doses/24 hours.
5. If converting from a long acting opioid, give the first methadone dose 6 hours after the last long acting opioid dose or 10- 12 hours after opioid patch removal. Consider using an alternative short acting opioid (such as Oramorph) for breakthrough pain management and consider reduction of the previous breakthrough dose to 50%.

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

If excess sedation occursreduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission.

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

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

Notes:

- Not licensed for use in children.
- Methadone is a racemic mixture: L-isomer, analgesic active (levomethadone; L-polamidon®); R-isomerunknown action.
- In some countries levomethadone is available. It has a different strength to methadone.
- Data on methadone in paediatric patients is limited; known to have wide inter-individual pharmacokinetic variation.
- Use methadone with caution, as methadone's effect on respiration lasts longer than analgesic effects.
- Side effects are the same as for all strong opioids.
- Following concerns regarding methadone and sudden death from prolongation of QT

interval or torsade de pointes (especially at high doses) it is recommended that patients have an ECG prior to initiation of treatment and regularly whilst on methadone, particularly if they have any risk factors or are having intravenous treatmentwith methadone.

- Opioid antagonists naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent individuals. Naloxone will also antagonise the analgesic, CNS and respiratory depressant effects of methadone.
- Methadone has the potential for a number of significant drug interactions. Drugs that induce cytochrome P450 3A4 enzymes (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin and some HIV drugs) will increase the rate of metabolism of methadone and potentially lead to reduced serum levels. Drugs that inhibit the system (e.g. amitriptyline, ciprofloxacin, fluconazole) may lead to increased serum levels of methadone.
- Renal impairment: if severe (i.e.GFR <10 ml/min or serum creatinine >700 mmol/l) – reduce methadone dose by 50% and titrate according to response. Significant accumulation is not likely in renal failure, as elimination is primarily via the liver.
- As methadone has a long half-life, infusion of naloxone may be required to treat opioid overdose.
- Available as: linctus (2 mg/5 mL), mixture (1 mg/mL), oral solution (1 mg/mL, 5 mg/mL, 10 mg/mL, and 20 mg/mL), tablets (5 mg), and injection (10 mg/mL, 50 mg/mL, 50 mg/2 mL).
- Schedule 2 CD.

Evidence: [1, 2, 4, 5, 11, 48, 89, 354-369]

Methylnaltrexone

Use:

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

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

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

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

Notes:

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

Evidence: [1, 206, 370-375]

Metoclopramide

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

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

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

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

Use

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

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

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

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

Notes:

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

Evidence: [1-3, 10, 89, 91, 93, 96, 153, 155, 376-380]

Metronidazole topically

Use:

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

Dose and routes
By topical application:

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

Notes:

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

Evidence: [1, 2, 381, 382]

Miconazole oral gel

Use:

- Oral and intestinal fungal infection.

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

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

Prevention and treatment of intestinal candidiasis

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

Notes:

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

Evidence: [2, 383-385]

Midazolam

Use:

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

Dose and routes

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

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

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

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

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

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

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

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

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

By buccal or intranasal administration

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

By rectum

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

By intravenous or subcutaneous injection
The dosages below are based on the BNFc [2]. However research evidence and adult formularies [5] suggests that buccal/intranasal and subcutaneous injections have very similar bioavailability. Many units therefore will use doses of 100 micrograms/kg.

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

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

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

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

Use 25-50% of the conscious sedation dose.

Notes
- Buccal (Buccolam oromucosal solution) midazolam is not licensed for use in infants less than 3 months of age. Midazolam injection is not licensed for use in seizure control or anxiety.Not licensed for use in children less than 6 months for premedication and conscious sedation.
- The range of potential indications for midazolam in paediatric palliative care is very wide, but most are not licensed in infants in children. Please see product literature.
- Recommended SC/IV doses vary enormously in the literature. If in doubt, start at the lowest recommended dose and titrate rapidly.
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 mins.Half life 2-5 hours. For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Onset of action by oral or gastrostomy route 10-30 minutes. If enteral tube administration is indicated, the oral liquid or injection can be used.
- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Both high and low doses can lead to paradoxical agitation.
- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency.
- Important drug interactions:Midazolam is a major substrate of CYP3A4. Please refer to current edition of BNF for significant drug interactions. Fatalities have occurred after concurrent administration with higher than approved doses of olanzapine
- Available as: oral solution (2 mg/mL special import USA, unlicensed), buccal liquid (pre-filled oral syringes 10 mg in 2 mls; 7.5 mg in 1.5 mls; 5 mg in 1 mL; 2.5 mg in 0.5 mlsBuccolam$^{(R)}$), and injection 1mg/mL, 2mg/mL, 5mg/mL).
  Other oral and buccal liquids (e.g.Epistatus$^{(R)}$ 10 mg/ml) are also available from 'specials' manufacturers or specialist importing companies (unlicensed).
- The buccal and oral formulations available may differ in strength – take care with prescribing.
  Schedule 3 CD (CD No Register Exempt Safe Custody)

Evidence: [2, 6, 145, 147, 149, 385-392]

Morphine

Use:

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

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

By mouth or by rectum

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

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

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

By continuous SC or IV infusion:

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

Breakthrough pain

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

Dyspnoea
30-50% of the dose used for pain.

Notes:

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

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

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

Evidence: [1-3, 6, 10, 46, 48, 144, 171, 253, 393-412]

Nabilone

Use:

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

Dose and routes
By mouth:

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

Notes:

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

Evidence: [1, 2, 5, 413-415] ARE

Naloxone

Use:

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

Dose and routes

Complete reversal of respiratory depression due to acute opioid overdose

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

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

By continuous intravenous infusion, adjusted according to response

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

Notes

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

Evidence: [2, 416, 417] ARE

Naproxen

Uses:

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

Dose and route:
By mouth

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

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

Notes:

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

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

Evidence: [1, 2, 5, 10]

Nystatin

Use:

- Oral and perioral fungal infection.

Dose and routes
By mouth:

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

Notes:

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

Evidence: [2, 191, 418]

Octreotide

Use:

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

Dose and routes
By subcutaneous injection

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

By continuous intravenous or subcutaneous infusion

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

Notes:

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

Evidence: [2, 89, 419]

Olanzapine

Uses:

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

Dose and route**:**
Oral:

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

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

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

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

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

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

Notes:

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

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

Evidence: [1, 2, 420-436]

Omeprazole

Use:

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

Dose and routes
By mouth:

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

Intravenous (by infusion over 20-30 minutes)

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

Notes:

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

Evidence: [1-3, 10, 304, 437-443]

Ondansetron

Use:

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

Dose and routes

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

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

By intravenous infusion over at least 15 minutes

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

By mouth following intravenous administration

Note:
Oral dosing can start 12 hours after intravenous administration

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

Nausea and vomiting

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

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

Notes:

- Ondansetron injection is licensed for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of post operative nausea and vomiting (PONV) in children (as a single dose) aged ≥1 month. Oral ondansetron is licensed from 6 months of age

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

Source: [2, 3, 6, 90, 142, 377, 444-447]

Oxycodone

Use:

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

Dose and routes

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

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

By mouth:
Conversion

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

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

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

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

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

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

Notes:

- Not licensed for use in children less than 12 years of age.
- No neonatal dose available.
- No evidence of any benefit over morphine and significantly more expensive.
- Associated with dose dependant QTc prolongation.
- Available in combination with naloxone as alternative to laxative therapy in opioid-induced constipation Targinact® (Napp) – not licensed in children.
- It is important to prescribe breakthrough analgesia which is 5-10% of the total 24 hour dose, given every 1 to 4 hours.
- It is moderately different from morphine in its structure, making it a hypothetical candidate for opioid substitution.
- Caution in hepatic or renal impairment.
- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with WFI, 0.9% sodium chloride or 5% glucose.

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

Evidence: [1, 2, 5, 10, 54, 168, 448-455]

Oxygen

Use

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

Dose and routes:
By inhalation through nasal cannula

- Flow rates of 1– 2.5L/min adjusted according to response. This will deliver between 24–35% oxygen depending on the patient's breathing pattern and other factors. Lower flow rates may be appropriate particularly for preterm neonates.

By inhalation through facemask

- Percentage inhaled oxygen is determined by the oxygen flow rateand/or type of mask. 28% oxygen is usually recommended for continuous oxygen delivery.

Notes:

- The evidence to support the use of O2 in non-hypoxemic patients is scant at best, which is why it best to use it in an N of 1 fashion. The patient will say if it works or not. General experience is that response to O2 for the treatment of breathlessness is just as likely/unlikely regardless of the patient's PaO2, so try it and if it doesn't help stop.
- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Where self-report is not possible observation of the work of breathing is a more reliable indicator of breathlessness.
- Frequent or continuous measurement of oxygen saturations may lead to an over-reliance on technical data and distract from evaluation of the child's overall comfort, symptom relief and wellbeing.
- Target oxygen saturations of 92 – 96% may be appropriate in acute illness but are not necessarily appropriate for palliative care. More usual target oxygen saturations are above 92% in long-term oxygen therapy and 88-92% in children at risk of hypercapnic respiratory failure. Lower saturation levels may be tolerated in children with cyanotic congenital heart disease.
- It is important to be clear about the overall aims of oxygen treatment and realistic saturation levels for an individual child, as this will affect decisions about target oxygenation.
- In cyanotic congenital heart disease, oxygen has little effect in raising SaO2 and is not generally indicated. Pulmonary hypertension, in the early stages, may respond to oxygen, so it may be appropriate in the palliative care setting.
- Moving air e.g. from a fan maybe equally effective in reducing the sensation of breathlessness when the child is not hypoxaemic.
- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions. However continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.
- Oxygen administration via a maskor via NIPPV can be claustrophobic and/or damage facial skin. This can be reduced by using a nasal mask.The duration of supply from an oxygen cylinder will depend on the size of the cylinder and the flow rate.
- An oxygen concentrator is recommended for patients requiring more than 8 hours oxygen therapy per day.
- Liquid oxygen is more expensive but provides a longer duration of portable oxygen supply. Portable oxygen concentrators are now also available.

- If necessary, two concentrators can be Y-connected to supply very high oxygen concentrations.
- Higher concentrations of oxygen are required during air travel.
- Home oxygen order forms (HOOF) and further information available from www.bprs.co.uk/oxygen.html
- A secondary supply of oxygen for children spending a prolonged time away from home requires a second HOOF available from the above website e.g. short breaks, holiday or extended periods with other relatives.

Evidence: [1, 2, 5, 456-461]

Pamidronate (Disodium)

Use:

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

NB Seek specialist advice before use.

Dose and routes

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

By IV infusion

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

Formalignant hypercalcaemia: **(Seek specialist advice)**

By IV infusion

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

For osteogenesis imperfecta

By IV infusion

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

Notes:

- Not licensed for use in children.Well tolerated by children, but long term effects unknown.
- Local guidelines vary. Some centres advise DEXA scan and investigations into calcium metabolism before and after treatment. Effectiveness of Pamidronate in bone pain does not necessarily depend on demonstrating osteoporosis, but demonstration that iatrogenic osteopetrosis has not developed afterwards can be

reassuring.Flu-like symptoms often accompany first infusion, though typically do not recur with subsequent doses.

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

Evidence: [1, 5, 462-471]

Paracetamol

(US: Acetaminophen)

Use:

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

Dose:

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

Oral:

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

Rectal:

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

IV: as infusion over 15 minutes

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

Notes:

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

Evidence: [1-3, 6, 10, 247, 472-475]WRE

Paraldehyde (rectal)

Use:

- Treatment of prolonged seizures and status epilepticus.

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

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

Notes:

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

Evidence: [2, 6, 476-482] WRE

Phenobarbital

Use:

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

Dose and routes

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

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

Subcutaneous or intravenous injection or infusion:

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

Epilepsy:
By mouth:

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

Notes:

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

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

Evidence: [2, 3, 149, 206, 483]

Phenytoin

Use:

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

Dose

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

Oral or slow IV injection:

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

Status epilepticus, acute symptomatic seizures:

Slow IVinjection or infusion:

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

Notes:

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

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

Evidence: [2, 3, 5, 6, 10, 66, 451, 484-488], WRE

Phosphate (rectal enema)

Use:

- Constipation refractive to other treatments.

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

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

Fleet^{R}Ready to Use enema:

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

Notes

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

Evidence: [1, 2, 489-493], WRE

Pregabalin

Use:

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

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

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

Neuropathic Pain

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

Gabapentin to Pregabalin switch for neuropathic pain
Consult appendix 3

Notes:

- Not licensed for use in children or adolescents less than 18 years of age.
- Licensed in adults as adjunctive therapy for partial seizures; for the treatment of peripheral and central neuropathic pain and for the treatment of generalised anxiety disorder.
- NICE Guidance CG173 (Neuropathic pain in adults) recommends: ‘offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment of neuropathic pain, if the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs and consider switching again if the second and third drugs tried are also not effective or not tolerated’.
- MHRA/CHM issued a warning to prescribers in April 2019, advising on the risk of pregabalin abuse and dependence. Pregabalin re-classified as a Schedule 3 controlled drug. Be aware also of potential serious risks of interaction between pregabalin and other medicines that can cause CNS depression, particularly opioids.
- Pregabalin binds to the alpha-2 subunit of voltage gated calcium channels in the CNS thus inhibiting the release of excitatory neurotransmitters.
- Pregabalin has a binding affinity 6x greater than that of gabapentin.
- Oral bioavailability 90% or greater; can be taken with or without food. Peak plasma concentrations occur within 1.5 hours.
- Limited pharmacokinetic data in children suggests total exposure to pregabalin to be 30% lower in paediatric patients of weight <30kg (compared to those of weight 30kg or greater) due to increased drug clearance. Terminal half-life averaged 3-4 hours in children up to 6 years of age and 4-6 hours in those aged 7 years or older.

- Pregabalin does not bind to plasma proteins. It undergoes negligible liver metabolism nor does it affect the major CYP450 enzymes and therefore is unlikely to have significant drug interactions.
- Pregabalin is predominantly excreted unchanged by the kidneys and thus accumulates in renal impairment. Dose reduction is necessary in patients with renal impairment.
- No dosage adjustment is needed in hepatic impairment.
- Case reports of more profound psychological side effects with pregabalin than gabapentin.
- For administration via an enteral tube preferably use the oral solution. There are no specific data on the jejunal administration of pregabalin. Administer using the oral solution and monitor for loss of effect or increase in side-effects.
- Most commonly reported adverse effects are dizziness, somnolence and headache. These are generally transient and mild to moderate in nature and may be minimised by a gradual increase to the therapeutic dose.
- Available as: oral capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg and oral solution 20 mg/ml.
- Schedule 3 controlled drug although exempt from safe storage requirements.

Evidence: [1, 494-498] WRE

Promethazine

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

Use:

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

Dose and routes (for promethazine hydrochloride)
By mouth:

Symptomatic relief of allergy:

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

Sedation (short term use):

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

Nausea and vomiting (particularly in anticipation of motion sickness)

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

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

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

Notes:

- Phenothiazine antihistamine (anti H1) with moderatemuscarinic and D2 receptor antagonism. Has also been used orally for dyspnoea in adults.
- Not licensed for sedation in children under 2 years
- Used in neonatal units on bigger babies for oral sedation when usual IV sedationoptions not working. Note drug interactions, particularly causing increased antimuscarinic and sedative effects.
- Caution in epilepsy, asthma, renal and severe hepatic impairment. Risk of hypotension if co-prescribed with opioid.
- Note when prescribing, subcutaneous dose should be lower than corresponding oral dose due to significant first pass metabolism.
- Promethazine is *not* generally recommended for subcutaneous administration due to the risk of local necrosis, but diluted in an adequate volume of sodium chloride 0.9% can usually be administered by CSCI over 24 hours. Do *not* give bolus SC injections.
- Oral preparation can be effective for up to 12 hours (peak plasma concentration 2-3 hours after administration). Drowsiness may wear off after a few days of treatment.

- For use by feeding tube: the elixir is slightly viscous. No further dilution is necessary, for intragastric administration, but dilute with an equal volume of water for intrajejunal administration, or to reduce viscosity and resistance to flushing. Tablets will disintegrate if shaken in water for 5 minutes.
- Available as: promethazine hydrochloride tablets (10 mg, 25 mg), oral elixir (5 mg/5 mL), and injection (25 mg/mL). (Promethazine teoclate tablets also available, 25 mg, licensed for nausea, vertigoand labyrinthine disorders. Slightly longer acting than promethazine hydrochloride and dosing slightly different).

Evidence: [2, 3, 10, 405, 499], NoRE, ARE

Ranitidine

Use:

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

Dose and routes
By mouth:

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

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

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

Notes:

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

Evidence: [1-3, 5, 10, 500-503]

Risperidone

Use:

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

Dose and routes
Oral:

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

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

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

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

Notes

- Risperidone is a dopamine D2, 5-HTA, alpha-1 adrenoceptor and histamine-1 receptor antagonist.
- Risperidone is licensed for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years, using the doses above. Not licensed for use in children for mania, psychosis or autism (use different doses under specialist supervision).
- 99% bioavailable. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half-life 24 hours. Duration of action 12-48 hours.
- Caution in epilepsy (lowers seizure threshold) and cardiovascular disease; extrapyramidal symptoms less frequent than with older antipsychotic medications; can cause orthostatic hypotension; withdraw gradually after prolonged use.
- Risperidone can cause significant weight gain. Other common side effects include anxiety, depression, sleep disorders, hypertension, oedema, malaise.
- Initial and subsequent doses should be halved in renal or hepatic impairment.
- Oral liquid is the preferred preparation for administration via enteral feeding tubes. Tablets also disintegrate in water within 5 minutes for easy administration via enteral feeding tubes.There is no specific data relating to jejunal administration of risperidone. Administer using the above method. Monitor for

loss of efficacy or increased side-effects.The oral liquid may be diluted in any non- alcoholic drink except tea.

- Available as: tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg, 6 mg), orodispersible tablets (500 microgram, 1 mg, 2 mg, 3 mg, 4 mg),oral solution 1 mg/mL.

Evidence: [2, 10, 224, 504-509] NoRE

Salbutamol

Use:

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

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

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

Aerosol inhalation:

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

Nebulised solution:

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

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

Notes

- Salbutamol is a short acting beta 2 adrenergic receptor agonist.
- Salbutamol is not licensed for use in hyperkalaemia; injection is not licensed for use in children.
- In palliative care, if airflow obstruction is suspected, a pragmatic approach may be to give a trial (e.g. 1–2 weeks) of a bronchodilator and evaluate the impact on symptoms. Spirometry should normally be used to confirm a possible underlying asthma diagnosis.
- Clinical efficacy of salbutamol in infants <18 months is uncertain, presumably due to the immaturity of the receptors; ipratropium may be more helpful in those less than 1-2 years.
- For an acute episode, many paediatricians now advise multi-dosing of salbutamol 100microgram up to 10 times, via a spacer where practicable for the patient instead of a nebuliser.
- Onset of action 5 minutes inhaled, 3-5 minutes nebulised. Peak response 0.5-2 hours.Duration of action 4-6 hours. Only 10-20%of inhaled dose reaches lower airways.
- Side effects: increased heart rate; feeling “edgy” or agitated; tremor.

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

Evidence: [1-3, 510-515]

Senna

Use:

- Constipation

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

Syrup:

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

Tablets:

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

Notes:

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

Evidence: [1, 2, 6, 10, 155, 492, 516-519]

Sodium Citrate

Use:

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

Dose and routes

Micolette Micro-enema

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

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

Micralax Micro-enema

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

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

Relaxit Micro-enema

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

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

Notes

- Sodium citrate is an osmotic agent. Sodium lauryl sulfoacetate is a faecal softener.
- As micro-enema, often used in combination with oral laxatives, particularly in neuromuscular disorders, faecal loading and faecal impaction.
- Usually acts within 15 minutes of administration.
- Contraindicated in acute gastro-intestinal conditions.
- Caution: can cause harmful sodium and water retention in susceptible patients.
- Available as: micro-enema (5 mL). All currently marketed preparations include sodium citrate 90 mg/ml, but other constituents vary.
- NICE Guidance for the management of constipation in children and young people advocated the use of polyethylene glycol 3350 containing laxatives and stimulant laxatives before the use of rectal measures. Sodium Citrate is considered the first line rectal measure, in preference to phosphate enemas.

Evidence: [1, 2, 492, 517-519]

Sodium Picosulfate

Use:

- Constipation (stimulant laxative).

Dose and routes:
By mouth:

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

Notes

- Elixir is licensed for use in children; capsules are not licensed for use in children less than 4 years of age.
- Acts as a stimulant laxative.
- NICE Guidance CG99: Constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives prior to a trial of a stimulant laxative.
- Onset of action 6-12 hours.
- Contraindicated in intestinal obstruction and dehydration.
- Effectiveness dependent upon breakdown by gut flora – previous effectiveness may therefore be lost during courses of antibiotics and ensuing altered gut flora.
- For administration via an enteral feeding tube: use the liquid preparation; dilute with an equal volume of water. Sodium picosulfate reaches the colon without any significant absorption; therefore, the therapeutic response will be unaffected by jejunal administration.
- Available as: elixir (5 mg/5 mL) and capsules (2.5 mg).

Evidence: [1, 2, 10, 492, 517-519]

Sucralfate

Use:

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

Dose and route:

Oral

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

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

Topical

For haemostasis

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

Notes:

- Complex of aluminium hydroxide and sulphated sucrose. In the gut it seems to act by protecting mucosa from acid-pepsin attack. Minimal antacid properties.
- Sucralfate acts locally and is minimally absorbed.
- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration.
- Spread doses evenly throughout waking hours.
- Following reports of bezoar formation associated with sucralfate, the CSM has advised caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.
- Caution – absorption of aluminium from sucralfate may be significant in patients on dialysis or with renal impairment.
- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by **at least** 1 hour to avoid formation of an insoluble complex that may block fine-bore feeding tubes. By mouth sucralfate should be given 1 hour before mealsto reduce chance of bezoar formation. Suggest diluting with water before administration. Not appropriate for jejunal administration as the site of action is gastric and duodenal.
- Tablets may be crushed and dispersed in 10-15 mL water.
- Available as: oral suspension (1 g in 5mL special order), tablets (1 g).Oral suspension, cream, powder and enema available as special order.

Evidence: [1, 2, 5, 6, 10, 520-525]

Sucrose

Use:

- Analgesia for procedural pain in babies.

Dose and routes:
By mouth:

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

Notes

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

Evidence:[3, 526-530]

Tapentadol

Use:

- Opioid analgesic

Dose and Route:

Opioid naïve patient: Use the following initial doses

By mouth;

Moderate to severe acute pain (using immediate release preparations)

- **Child 2-17 years (body-weight >16 kg):** 1.25 mg/kg/dose every 4 hours (maximum single dose 50 mg), the dose for children with a high BMI must not exceed the calculated dose for a body-weight at the 97.5 percentile for the given age.The maximum dose per day is 7.5mg per kg body weight (≙ 6 x single dose)(*see notes below)
- **18 years and older:** Initially 50 mg every 4–6 hours, adjusted according to response, on the first day of treatment, an additional dose of 50 mg may be taken 1 hour after the initial dose; maximum 700 mg in the first 24 hours; maximum 600 mg per day.

Severe chronic pain (using modified-release preparations)

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

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

Notes:

- Dual action centrally acting opioid analgesic; agonist at the μ-opioid receptor and inhibitor of noradrenaline reuptake. The latter enhances the action of the descending pain inhibitory pathway contributing to a synergistic analgesic effect.
- *Tapentadol oral solution is licensed for the relief of moderate to severe acute pain in children from 2 years of age (>16 kg body weight) for a maximum of 72 hours. Use of tablet formulations or for treatment of chronic pain or for a duration >72 hours in children is off-label. Data on safety and efficacy of long-term use in children is not yet available and clinical trials are on-going.
- Tapentadol oral solution, immediate-release and modified-release tablets are licensed in adults for treatment of moderate to severe acute and chronic pain.
- Tapentadol can be taken with or without food.
- Tapentadol oral solution 20 mg/mL can be taken undiluted or diluted in water or any non-alcoholic drink. Use the dosing pipette (5ml subdivided in 0.1ml (2mg) intervals) provided to ensure the exact dose can be accurately measured.
- Tapentadol oral solution can be administered via an enteral feeding tube.
- Tapentadol oral solution contains 2 mg/mL propylene glycol.
- Modified-release tapentadol tablets should be swallowed whole; crushing or chewing will lead to a rapid release of an overdose of tapentadol.
- Dosage adjustment is not required in mild or moderate renal impairment. Use is not recommended in severe renal impairment.
- Dosage adjustment is not required in mild hepatic impairment. Reduce initial dose in moderate hepatic impairment. Use is not recommended in severe hepatic impairment.

- Based on immediate release tablets – onset of action is less than 1 hour with time to peak serum concentrations around 75 minutes. Duration of action 4-6 hours. Duration of action of modified-release tablets is 12 hours.
- Tapentadol is rapidly and completely absorbed after oral administration. However mean absolute bioavailability after a single-dose administration is ~32% due to extensive first-pass metabolism.
- The major elimination pathway for tapentadol is glucuronide conjugation. Tapentadol does not have any active metabolites. The potential for drug-drug interactions is low. Plasma protein binding is low.
- Potential adverse effects as for other opioids. However GI side-effects are reportedly less than with oxycodone or morphine.
- MHRA/CHM advice: Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines (January 2019). Tapentadol can induce seizures and should be prescribed with caution in patients with a history of seizure disorders or epilepsy. Seizure risk may be increased in patients taking other medicines that lower seizure threshold, for example, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics.
- Care needed if switching from another μ-agonist to tapentadol as this may cause low-grade opioid withdrawal. As required doses of the original opioid should be used to counter this (e.g. give an immediate release product at 25-50% of the original dose).
- Available as (all Schedule 2 CD)
- Oral solution 20 mg/mL (licensed from 2 years) Palexia®
- Immediate-release tablets 50 mg, 75 mg (licensed from 18 years only) Palexia®
- Modified-release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg (licensed from 18 years only) Palexia®

Evidence: [2, 5, 531-536]

Temazepam

Use:

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

Dose and routes
By mouth,

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

Notes:

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

Evidence: [1, 2, 5, 10]

Tizanidine

Use:

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

Dose and routes
Children doses based on WRE

- **Child 18 months–6 years:** 1 mg/day; increase if necessary according to response.
- **Child 7-11 years:** 2 mg/day; increase if necessary according to response.
- **Child >12 years:** as per adult dose [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.

Children doses based on

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

Notes:

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

Evidence: [1, 10, 37, 42, 537-542]

Tramadol

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

Use:

- Minor opioid with additional non-opioid analgesic actions.

Dose and routes
By mouth:

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

By IM or IV injection or infusion:

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

Notes:

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

Evidence: [1, 2, 10, 48, 65, 409, 543-546]

Tranexamic acid

Use:

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

Dose and routes
By mouth:
Inhibition of fibrinolysis

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

Menorrhagia

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

By intravenous injection over at least 10 minutes:

Inhibition of fibrinolysis

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

By continuous intravenous infusion:

Inhibition of fibrinolysis

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

By other routes

Mouthwash 5% solution:

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

Topical treatment:

- Apply gauze soaked in 100mg/mL injection solution to affected area.

Notes:

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

Evidence: [2, 6, 547-552]

Trihexyphenidyl

Uses:

- Dystonias; Sialorrhoea (drooling); Antispasmodic.

Dose and route:
By mouth

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

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

Notes:

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

Reference: [1, 2, 10, 216, 553-561]

Vitamin K (Phytomenadione)

Use:

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

Dose and routes
By mouth or intravenous:

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

Notes:

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

Evidence:[1, 3, 6]

Appendix 1: Morphine equivalence single dose

[1, 2, 5, 419]

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

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

Appendix 2: Subcutaneous infusion drug compatibility

Evidence suggests that during end of life care in children, where the enteral route is no longer available, the majority of symptoms can be controlled by a combination of six “essential drugs” [562].

Ketamine can be used as an opioid adjuvant, on the advice of a specialist, and is useful for pain with a neuropathic component or to prevent opioid tolerance or opioid dose escalation [261]**.**

Compatibility for these six drugs is given in the table 1 below[5].

Water for injection is usually the standard choice of diluent to minimise the likelihood of incompatibility. However, NaCl 0.9% should be considered if inflammation at the injection site occurs as long as the drug combinations are compatible[5]. For more detailed information professionals are advised to consult an appropriate reference source[11]

Table 1: Syringe driver compatibility for two drugs in water for injection [5, 11, 563, 564]

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

*Data for oxycodone 10mg/mL injection. Oxycodone 50mg/mL has a differentcompatibility profile compared to the lower strength oxycodone and compatability should be considered separately and not extrapolated from one formulation to another[5].

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

Appendix 3: Gabapentin to Pregabalin Switch for Neuropathic Pain

Gabapentin and pregabalin have similer mechanisms of action (see APPM monographs). However, gabapentin absorption is saturable, leading to non-linear pharmacokinetics**,** whereas pregabalin possesses linear pharmacokinetics. As a consequence, switching between gabapentin and pregabalin is not straight-forward and there is very limited evidence in the literature with regard to managing a switch, with no evidence in children[565]. Nonetheless, many pain centres in the UK have developed local protocols for a switch in adults,with no reports of adverse effects [566, 567]. The following conversion factors have been used:

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

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

Table 2: Gabapentin to Pregabalin switch

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

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

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

Appendix 4: Benzodiazepines

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

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

(2) Comparative pharmacokinetic data.

Diazepam

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

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

Lorazepam

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

Midazolam

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

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1. = [1]
2. = [5]
3. = [6]

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