The Association for Paediatric Palliative Medicine

Formulary

6th edition

2024

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Every attempt has been made to ensure information presented in this formulary is accurate and up to date as of September 2023. Important updates or corrections will be posted on the APPM Formulary web-page which can be accessed by scanning the QR code.

The APPM Formulary editorial team welcomes feedback, comments, suggestions and recommendations from healthcare professionals in the UK and across the world. Please contact Lynda.Brook@alderhey.nhs.uk

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Foreword

The Association for Paediatric Palliative Medicine formulary has been the paediatric palliative care prescribers' best friend for over a decade and continues to go from strength to strength. It is now on its 6th edition with a change in the editorial leadership to Dr Lynda Brook supported by a new deputy editor Dr Ella Aidoo. This fresh perspective brings some welcomed new additions to support prescribing practice whilst maintaining the original core purpose of the formulary-to support prescribers working in paediatric palliative care. The formulary continues to provide prescriber guidance across the age range from neonates to adolescents.

Where available, and relevant to our clinical population, Medicines for Children leaflets on specific medication have been embedded. There has been an expansion in clinical indications for some medications with detailed guidance on use in some cases. There are several new additions; Codeine, Dihydrocodeine and several other monographs have been removed. Due to the welcomed growing evidence, some references will be separately held but accessible for the prescriber on the APPM website.

For opioid prescribing, there are conversion tables between routes of administration, breakthrough doses, pain in the opioid naive and example calculations to support the prescriber. Furthermore, Methadone receives more detailed guidance and direction. Practical compromise for Midazolam dosing has occurred in this edition with clearer dosing per route of administration.

The appendices have expanded to support knowledge and understanding in the management of medicines including opioid conversion tables and stewardship. There is some additional guidance on the administration of buccal medication, prolonged QT syndrome and switching medication in the same drug class (gabapentinoids and benzodiazepines).

Huge congratulations to Lynda and her team on a highly successful and ambitious expansion. Thank you also to all of those who have contributed to this, and previous editions. The formulary is largely an unfunded labour of love supported by an enthusiastic band of overstretched and underfunded colleagues working in the field of paediatric palliative care. It is a credit to them that they offer their expertise and valuable time due to their steadfast commitment to raising standards of care for the children with palliative care needs across the sector.

AK Anderson, September 2023.

Preface

Taking over as Editor for the APPM Formulary is a significant responsibility. Dr Sat Jassal is certainly a formidable act to follow!

When Sat raised his hand as I chaired the inaugural meeting of the Association for Paediatric Palliative Medicine in 2010 and suggested developing the APPM Master Formulary I don't think anyone could have imagined where this simple act would lead. Over the 12 years since the first edition of the formulary, it has grown to become a significant body of work providing definitive guidance on prescribing in paediatric palliative medicine to professionals in the UK and across the world. The first edition of the formulary, published in January 2011, contained monographs for 82 drugs with 202 references contained within 72 pages. This latest edition of the formulary includes monographs for 104 drugs, 410 references and comprises a total of 273 pages.

The growth of the formulary reflects other changes too: the increasing number of professionals working in paediatric palliative medicine in the UK and worldwide; the growth in non-medical prescribing; the increasing range of medicines available to prescribe with corresponding increases in the research evidence base to support their use; changes in technology allowing dissemination of information across the world wide web and most importantly the increasing number of children and their families benefitting from improvements in quality of life and quality of end of life care enabled through these advances.

As the new Editor, I am building on nearly 20 years of experience in paediatric palliative medicine, my original work on the first WHO list of Essential Medicines for Paediatric Palliative Care, my work as a contributor to the APPM Master Formulary and more recently my work as Deputy Editor under close support and supervision of Sat.

I would like to offer an enormous thank-you to Sat for all your hard work over the last 13 years from myself, colleagues in the UK and worldwide, and the thousands of children and their families whose lives have hopefully been made a little bit easier through the invaluable information presented in the formulary.

Here's to the next chapter.

Lynda Brook, September 2023

Contents

Introduction

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

Notable changes are as follows:

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

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

The Formulary, together with versions translated into other languages, is available to download from the Association for Paediatric Palliative Medicine website www.appm.org.uk

Lynda Brook and Anita Aindow, September 2023

Using the formulary

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

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

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

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

Patient information leaflets

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

Prolonged QT-interval

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

Relation to BNFC

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

Accuracy of information

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

We would strongly advise practitioners not to prescribe outside their expertise, and if in doubt to consult the growing network of clinicians with specialist expertise in paediatric palliative medicine via the Association of Paediatric Palliative Medicine.

Weight or age-based dosing

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

Abbreviations

$5HT_2$	5 hydroxytryptamine (serotonin) type 2 receptor
$5HT_3$	5 hydroxytryptamine (serotonin) type 3 receptor
APLS	Advanced Paediatric Life Support
ALT	Alanine transaminase
AST	Aspartate transaminase
CD	Controlled drug
CIVI	Continuous intravenous infusion
cLQTS	Congenital long Q-T syndrome
CNS	Central nervous system
COX	Cyclo-oxygenase
CSCI	Continuous subcutaneous infusion
CSF	Cerebrospinal fluid
GFR	Glomerular filtration rate
IM	Intramuscular
IV	Intravenous
kg	Kilograms
MAD	Mucosal atomiser device
mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Authority
ml	millilitres
NHS	National Health Service (UK)
NICU	Neonatal intensive care unit
NK	Neurokinin type 1 receptor
NMDA	N-methyl-D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
PICU	Paediatric intensive care unit
PO	By mouth (per oral)
PRN	As required
SC	Subcutaneous
SL	Sublingual
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
TdP	Torsades de Pointes
UK	United Kingdom
WFI	Water for injection
WHO	World Health Organisation

Formulary

Acetazolamide

Use:

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

Dose and route:

Epilepsy

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

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

Raised intracranial pressure

By mouth or slow intravenous injection:

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

Notes:

- Carbonic anhydrase inhibitor.

Licensing

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

Therapeutics

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

Contraindications, cautions

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

Side effects

- Association with acute kidney injury (AKI) in critically ill children admitted to intensive care units
- May cause electrolyte disturbance with prolonged use (can be corrected with potassium bicarbonate), gastrointestinal disturbance, paraesthesia at higher doses and haematological abnormalities.
- Monitor blood count and electrolytes in prolonged use.

Interactions

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

Administration

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

Available as

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

Evidence: (1–10)

Adrenaline (also known as Epinephrine)

Use:

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

Dose and route:

Localised bleeding:

By topical application

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

Upper airway obstruction:

By inhalation of nebulised solution:

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

Notes

Licensing

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

Side effects

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

Pharmacokinetics

- Nebulised: duration of action 2-3 hours

Available as

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

Evidence: (1–3,11)

Alfentanil

Use:

- Short acting synthetic lipophilic opioid analgesic derivative of fentanyl
- Alternative opioid in patients with end stage (4 or 5) renal failure, opioid related neurotoxicity or intolerance to other opioids
- Useful for breakthrough pain and procedure-related pain
- Used as analgesic especially intra-operatively and for patients in intensive care and on assisted ventilation (adjunct to anaesthesia)

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in patients already receiving regular strong opioids

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of opioid administered over the previous 24 hours

  Convert to the equivalent dose of alfentanil using the table below (see also Appendix 1)

- Consider reducing the dose of alfentanil by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Alfentanil CSCI or CIVI	30:1	Divide 24hour morphine dose by 30	Morphine oral 60mg/24hours ÷ 30 = alfentanil CSCI 2mg/24hours
Morphine CSCI or CIVI	Alfentanil CSCI or CIVI	15:1	Divide 24hour morphine dose by 15	Morphine CSCI 30mg/24hours ÷ 15 = alfentanil CSCI 2mg/24hours

Breakthrough pain in patients already receiving opioids

By subcutaneous, buccal and intranasal routes

- 1/10 to 1/6 (10%-16%) of the total CSCI dose as required, up to hourly

  There is no direct correlation between the effective PRN-dose and the regular background dose: start with low dose and titrate according to response

Procedure-related pain SEEK SPECIALIST ADVICE

By subcutaneous, buccal and intranasal routes

Administer at least 5 minutes before procedure, repeating if needed.

- **Child 2-11 years:** 5micrograms/kg single dose, maximum 250micrograms/dose
- **12 years and over**: 250-500micrograms single dose over 30 seconds. Subsequent doses 250micrograms

Notes:

Licensing

- Licensed for perioperative use in children. Not licensed for pain relief in palliative care. Not licensed for buccal, sublingual, or intranasal administration. Not licensed for incident or breakthrough pain.

Therapeutics

- Rapid onset of action (less than 5 minutes after subcutaneous bolus injection), and short duration of action (less than 60 minutes). Even with an optimally titrated PRN dose, frequent dosing (even every 1-2 hours) may be required. Review dose and frequency of administration regularly.
- Useful for incident and breakthrough pain as faster onset, shorter acting and smaller volumes required compared with fentanyl. Not appropriate for titration of opioid requirements against the patient's pain due to short duration of action. No direct correlation between the effective PRN dose and the regular background dose.
- Limited information or evidence for analgesic doses in palliative care, especially in children. Doses are largely extrapolated from suggested equianalgesic doses with other opioids.

- Useful in patients with severe renal failure (no dose reduction is needed). Avoid or reduce doses by 30-50% in severe hepatic impairment.
- Calculate starting doses in obese children based on ideal body-weight for height rather than actual body-weight.
- Potential alternative to diamorphine or fentanyl when higher doses of opiate are required but subcutaneous administration is difficult due to large volume of infusion.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Contraindications, cautions

- Contraindicated in patients receiving MAOIs (monoamine oxidase inhibitors) or within 2 weeks of their discontinuation.
- Greater risk of addiction, tolerance and drug seeking behaviour particularly when administered via buccal or intranasal routes, compared with longer acting opioids.

Side effects

- Usual opioid side effects, hypothermia and muscle rigidity (which can be managed with neuromuscular blocking drugs).

Pharmacokinetics

- Half-life prolonged in neonates: risk of accumulation. Clearance may be increased in patients from 1 month to 12 years of age: higher doses may be needed.

Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by CYP3A4 inhibitors including aprepitant, ciprofloxacin, clarithromycin, erythromycin and fluconazole. Levels reduced by CYP3A4 inducers including carbamazepine and phenobarbital. Levels potentially increased by midazolam.

Administration

- Compatible with sodium chloride 0.9% or dextrose 5% as a diluent. Physically compatible with most drugs used in a syringe driver. Possible concentration-dependent incompatibility with cyclizine: use water for injection as diluent and observe for crystallisation.

Available as

- Injection (500 micrograms/ml in 2ml, 10ml and 50ml ampoules); Intensive care injection (5mg/ml in 1ml ampoule to be diluted before use). Nasal spray with attachment for buccal / SL use (5mg/5ml bottle available as special order from Torbay Hospital Manufacturing Unit Tel: 01803 664707, torbaypharmaceuticals@nhs.net. Each ‘spray’ delivers 0.14ml = 140micrograms alfentanil. More costly than using injection preparation).

CD

- Schedule 2 CD

Evidence: (1–3,12,13)

Alimemazine (Trimeprazine) tartrate (NEW)

Use:

- Urticaria
- Pruritus
- Anti-emetic
- Procedural sedation
- Short term treatment of sleep disturbance in children with suspected or definite neurodevelopmental disorder where other behavioural and pharmacological measures have failed

Dose and route:

Doses as alimemazine *tartrate* (see notes below for other formulations)

Urticaria, pruritus, anti-emetic

By mouth

- **Child 6 months-1 year (specialist use only):** 250micrograms/kg, maximum 2.5mg/dose, 3–4 times daily
- **Child 2-4 years**: 2.5mg, 3–4 times daily
- **Child 5-11 years**: 5mg 3–4 times daily
- **12 years and over**: 10mg 2–3 times daily

Procedural sedation, night sedation

By mouth

1-2 hours before procedure or 1-2 hours before bed-time

- **Child 1 month-1 year (specialist use only):** 1-2mg/kg as a single dose
- **2 -11 years:** 1-2mg/kg not to exceed 60mg as a single dose
- **12 years and over**: Up to 30-60mg as a single dose

Notes:

Sedative phenothiazine antihistamine

Licensing

- Unlicensed for treatment of urticaria or pruritus in children from the age of 6 months to 2 years. Licensed for sedation in children from 2-6 years. Licensed indications may differ between formulations

Therapeutics

- Total daily doses of up to 100mg have been reported in adults

Contraindications, cautions

- Contraindicated in neonates and children under 2 years except on specialist advice, epilepsy.
- Caution in patients with cardiac disease and those with, or at risk of prolonged QT, hypotension or risk of hypotension; may lower seizure threshold; pyloroduodenal obstruction; urinary retention; hepatic impairment and/or jaundice

Side effects

- Respiratory depression, particularly at higher sedative doses, cardiac arrhythmia, mood and sleep disturbance, seizures, dystonia, photosensitivity especially at higher doses, neuroleptic malignant syndrome

Hepatic impairment, renal impairment

- Contraindicated in severe renal failure and severe hepatic failure

Interactions

- Sedative effects intensified when co-administered with other sedatives
- Increased antimuscarinic and sedative effects with anticholinergics including tricyclics, antihistamines and MAOIs
- Hypotensive effects intensified when co-administered with other hypotensive agents especially alpha adrenoreceptor blockers
- May reduce or abolish effects of clonidine

Administration

- Dilute oral solution or oral syrup with an equal volume of water before administration via feeding tube. Tablets can be crushed and mixed with water for administration. The blue film-coating can be washed off the tablets to make them easier to crush. Without crushing they disperse in one to two minutes. Flush tube well before and after administration
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy

Available as

- Oral syrup / liquid containing alimemazine tartrate 7.5mg/5ml, 10mg/5ml and 30mg/5ml; alimemazine tartrate 10mg tablets
- A variety of brands/generics available, and the syrup formulations contain high amounts of sucrose and ethanol. Check carefully. Oral solutions may be preferable to syrups in terms of sucrose and ethanol content. Liquid formulations may also contain methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed) and/or sodium sulfite anhydrous (E221) and sodium metabisulfite (E223), which may rarely cause severe hypersensitivity reactions and bronchospasm. Alimemazine tartrate is given orally; doses in the UK are given as the amount of alimemazine tartrate, while those in some other countries are expressed in terms of the equivalent amount of alimemazine. Alimemazine tartrate 25mg is equivalent to about 20mg of alimemazine

Evidence: (1,14–25)

Amitriptyline

Use:

- Neuropathic pain
- Drooling, sweating, refractory cough
- Neuropathic pruritus

Dose and route:

By mouth:

- **Child 2-11 years**: Initial dose of 200micrograms/kg (maximum 10mg) at night increased gradually, if necessary. Recommended maximum 1mg/kg/dose twice daily (under specialist supervision)
- **12 years and over**: Initial dose of 10mg at night increased gradually, if necessary, every 3-5 days to a suggested initial maximum of 75mg once daily

  Higher doses up to 150mg daily in divided doses may be used in adults under specialist advice.

  Twice daily dosing rarely needed. If necessary give 25-30% of daily dose in morning and 70-75% at night

Notes:

Licensing

- Not licensed for use in children with neuropathic pain or pruritus, drooling, sweating or cough.

Therapeutics

- Evidence of benefit for neuropathic pruritus in adults.
- Analgesic effect unlikely to be evident for several days. Improved sleep and appetite are likely to precede analgesic effect.
- Benefit generally increases with higher doses; however benefit is lost at higher doses in some patients.
- Benefit in cough probably relates to reduction in cough reflex hypersensitivity.

Contraindications, cautions

- Contraindicated in severe liver impairment.
- Contraindicated in patients receiving MAOIs (monoamine oxidase inhibitors) or within 2 weeks
- of their discontinuation.
- Caution in mild/moderate hepatic impairment, heart block and arrhythmias.
- Caution in epilepsy: may lower seizure threshold

Side effects

- Main side effects limiting use in children include: constipation, dry mouth, blurred vision and drowsiness.

Pharmacokinetics

- Absorbed slowly from gastrointestinal tract. Peak plasma concentration occurs 4-8 hours after oral administration.

Interactions

- Metabolised by cytochrome P450 enzymes CYP2D6 and CYP2C19. Levels increased by drugs that inhibit CYP2D6 enzymes including fluoxetine and fluconazole, particularly in those who are poor CYP2D6 metabolisers. Levels reduced by drugs that induce CYP2D6 enzymes including carbamazepine, phenobarbital and phenytoin.
- Carbamazepine reduces plasma amitriptyline by up to 60%.
- Amitriptyline increases the effects of adrenaline/epinephrine. Manufacturer advises avoid.
- May reduce effect of clonidine

Administration

- Oral solution may be administered via an enteral feeding tube (mix with equal volume of water; no data for some of the preparations). No specific data available for administration of tablets via enteral feeding tube.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet “Amitriptyline for neuropathic pain”: https://www.medicinesforchildren.org.uk/medicines/amitriptyline-for-neuropathic-pain/

Available as

- Tablets (10mg, 25mg, 50mg) and oral solution (10mg/5ml, 25mg/5ml, 50mg/5ml; other strengths may be available as ‘specials’).

Evidence: (1–3,8,26–30)

Aprepitant

Use:

- Prevention and treatment of nausea and vomiting associated with moderate or highly emetogenic cancer chemotherapy in combination with a corticosteroid (usually dexamethasone) and a 5-HT3 antagonist such as ondansetron
- Management of pruritus refractory to other treatment including paraneoplastic pruritus and drug related pruritus
- Cyclical vomiting
- Vomiting in gastrointestinal dystonia

Dose and route:

Chemotherapy induced nausea and vomiting

By mouth:

Day 1: 1 hour before chemotherapy

- **Child 6 months-11 years** (and not less than 6kg): 3mg/kg (maximum 125mg) as a single dose
- **12 years and over**: 125mg as a single dose

Days 2 & 3: 1 hour before chemotherapy or in the morning if no chemotherapy is given

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) as a single dose
- **12 years and over**: 80mg as a single dose

Cyclical vomiting (NEW)

By mouth:

Prodromal phase, at least 30 minutes before emetic phase

Child 6 months-11 years (and not less than 6kg): 3mg/kg (maximum 125mg) as a single dose

- **12 years and over**: 125mg as a single dose

Days 2 & 3

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) as a single dose
- **12 years and over**: 80mg as a single dose

Prophylaxis

Child 6 months-11 years (and not less than 6kg): 3mg/kg (maximum 125mg) twice weekly

- **12 years and over**: 125mg twice weekly

Vomiting in gastrointestinal dystonia refractory to other anti-emetics (NEW)

By mouth:

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) once daily
- **12 years and over**: 80mg once daily

Pruritus (NEW)

By mouth:

- **Child 6 months-11 years** (and not less than 6kg): 2mg/kg (max 80mg) once daily for 3-13 days. Then stop. If symptoms return, repeat course or reduce to alternate days.
- **12 years and over**: 80mg once daily for 3-13 days. Then stop. If symptoms return, repeat course or reduce to alternate days.

Notes:

- Selective high-affinity antagonist at neurokinin-1 (NK-1) receptors in vomiting centre and chemoreceptor trigger zone.

Licensing

- Licensed for the prevention of acute and delayed nausea and vomiting associated with highly or moderately emetogenic cancer chemotherapy in adults, children, and infants from 6 months of age (>6kg).

Therapeutics

- Powerful anti-emetic but may be significantly less effective in reducing nausea

Interactions

- Aprepitant is a substrate, a moderate inhibitor and an inducer of cytochrome P450 enzyme CYP3A4. Aprepitant is also an inducer of CYP2C9. During treatment with aprepitant CYP3A4 is inhibited. At the end of treatment aprepitant causes a transient mild induction of CYP2C9, CYP3A4 and glucuronidation
- Aprepitant therefore has the potential to interact with other drugs that are metabolised by these enzymes including alfentanil, buprenorphine, carbamazepine, dexamethasone, diazepam, diclofenac, domperidone, erythromycin, fentanyl, ibuprofen, midazolam and phenobarbital. *This list is not exhaustive-seek advice.*

Side effects

- Common: include hiccups, dyspepsia, diarrhoea, constipation, anorexia, asthenia, headache and dizziness.

Available as

- Capsules 80mg and 125mg and powder for an oral suspension (125mg powder yielding on reconstitution an oral suspension 25mg/ml).

Evidence: (1–3,31–37)

Arachis Oil Enema

Use:

- Faecal softener
- Faecal impaction

Dose and route:

By rectal administration

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

Notes:

Licensing

- Licensed for use in children.

Therapeutics

- Generally used as a retention enema to soften hard, impacted faeces. May be instilled and left overnight to soften the stool. Can be followed by use of a stimulant suppository or osmotic enema the following morning.

Contraindications, cautions

- Derived from peanuts, do not use in children with a known allergy to peanuts.
- Caution in inflammatory bowel disease and bowel obstruction.

Administration

- Warm enema in a water bath before use.
- Administration may cause local irritation.

Available as

- Enema, arachis (peanut) oil in 130ml single dose disposable packs.

Evidence: (1–3)

Atropine

Use:

- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation

Dose and route:

By sublingual route:

- **Neonate**: 20-40micrograms/kg/dose 2-3 times daily as required
- **Infant body-weight less than 10Kg:** 20-40micrograms/kg/dose 2–3 times daily as required
- **Child body-weight 10-19kg**: 250micrograms/dose 2–3 times daily as required
- **Child body-weight 20kg and over**: 250-500micrograms/dose, 2–3 times daily as required
- **12 years and over:** 500micrograms–1mg/dose 3-4 times daily as required

Use solution for injection 400 micrograms/ml, 600 micrograms /ml or 1mg/ml for administration of doses up to 250micrograms

Use 1% atropine eye drops (atropine 10mg/ml) for doses of 500micrograms and over.
1 drop of 1% atropine contains approximately 500micrograms of atropine

Notes:

Licensing

- Not licensed for this indication or route of administration.

Therapeutics

- Research evidence based on 0.5% eye drops, only available outside the UK.
- Use only where symptom is affecting quality of life. Used 3rd line if glycopyrronium bromide or hyoscine hydrobromide are either unavailable or ineffective.
- Monitor for anticholinergic side effects: concurrent treatment with 2 or more antimuscarinic drugs increases risk of side effects, central toxicity and worsening quality of life. Children are particularly susceptible.

Pharmacokinetics

- Bioavailability of sublingual atropine is approximately 60%

Side effects

- May result in central nervous system stimulation.

Available as

- Available in UK as 1% (10mg/ml) eye drops (10 ml or 0.5ml pack size). Outside the UK 0.5% eye drops are also available. Solution for injection 400 micrograms/ml, 600 micrograms /ml, 1mg/ml ampoules. Pre-filled syringes: 500micrograms/5ml, 1mg/5ml and 3mg/10ml.

Evidence: (1–3,11,38–53)

Baclofen

Use:

- Chronic severe spasticity and skeletal muscle spasm
- Dystonia
- Considered as third line for neuropathic pain
- Intractable hiccups

Dose and route:

By mouth:

Initial dose

- **Child 1 month and over**: 300micrograms/kg/day in 3-4 divided doses,

  Increased gradually every 3-7 days to a usual maintenance dose of

  - 750micrograms-2mg/kg/day in divided doses

  Maximum daily doses:

  - **Child 1 month-7 years**: 40mg/day in divided doses
  - **8 years and over**: 60mg/day in divided doses

By intrathecal injection:

- **Specialist teams only**. Maintenance 25-200micrograms daily via intrathecal pump.

Notes:

Licensing

- Oral preparations licensed for treatment of spasticity and skeletal muscle spasm for all ages. Intrathecal injection licensed from 4 years of age.

Therapeutics

- Review treatment for spasticity if no benefit within 6 weeks of achieving maximum dose and withdraw over at least 1-2 weeks, more gradually if symptoms occur, if ineffective.
- Less likely to result in dependence or tolerance than diazepam.
- Doses starting at approximately 50% of those for spasticity have been used in severe intractable hiccups. May have direct effect on diaphragm.
- Impact of undesirable hypotonia may be minimised by reducing daytime and increasing evening doses.
- Intrathecal use by specialist only, for severe chronic spasticity that cannot be effectively managed by enteral treatment.
- Intrathecal injection can be administered as a short term CSCI to avoid sudden withdrawal when enteral and/or intrathecal routes are unavailable.

- Abrupt withdrawal, including through loss of the enteral route, intrathecal or pump failure can precipitate life threatening withdrawal syndrome with hyperactivity, increased spasticity, autonomic dysfunction and serious psychiatric reactions.
- Limited clinical data on the use of baclofen in children under the age of one year.

Side effects

- Common: drowsiness, nausea, hypotonia. Potential effects on swallow, airway protection, posture and function. Exacerbation of epilepsy. Increased gastric acid secretion.

Contraindications, cautions

- Contraindicated in active peptic ulcer disease.

Hepatic impairment, renal impairment

- Risk of toxicity in renal impairment; use smaller oral doses and increase dosage interval if necessary.

Pharmacokinetics

- Oral bioavailability >90%, onset of action hiccup 4-8hours, muscle spasm 1-2 days, spasticity 3-4 days

Administration

- Administer after food to reduce risk of gastric irritation.
- May be administered via enteral feeding tubes including gastrostomy or jejunostomy. (Specific data only available for some makes of liquid and tablet). Use liquid formulation for small doses; dilute prior to use to reduce viscosity. Consider dispersing tablets in water for higher doses owing to the sorbitol content of the liquid formulation. (Teva brand tablets produce a fine dispersion in 10 ml water).

Patient information

- See Medicines for Children leaflet “Baclofen for muscle spasm”: https://www.medicinesforchildren.org.uk/medicines/baclofen-for-muscle-spasm/

Available as

- Tablets (10mg) and oral solution (5mg/5ml, 10mg/5ml). Solution for injection 50mg/ml. Intrathecal solution for infusion 500 micrograms/ml and 2mg/ml.

Evidence: (1,2,8,54–56,56–58)

Bethanechol

Use:

- Urinary retention including opioid-induced urinary retention

Dose and route:

By mouth:

- **Child 1-11 years**: 600micrograms/kg/day in 3 or 4 divided doses. Increasing if necessary and tolerated to a maximum of 1.2mg/kg/day in 3 or 4 divided doses. Maximum 10mg/dose.
- **12 years and over**: 10-25mg per dose 3 to 4 times daily. Increasing if necessary and tolerated to maximum of 50mg/dose

Notes

- Stimulates the parasympathetic nervous system, increasing bladder muscle tone and causing contractions which initiate urination.

Licensing

- Not licensed for use in children.

Contraindications, cautions

- Contraindicated in hyperthyroidism, peptic ulcer disease, asthma, cardiac disease and epilepsy.
- Safety and efficacy not established in children.

Interactions

- Effects antagonised by antimuscarinic agents

Pharmacokinetics

- Poorly absorbed by gastrointestinal tract. Therapeutic effect seen within 1 hour of oral administration.

Administration

- Administer 1 hour before or 2 hours after food to reduce likelihood of nausea and vomiting.
- Tablets may be crushed and dispersed in water for immediate administration via an enteral feeding tube; formulation for extemporaneous oral suspension is available.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- 10mg and 25mg tablets licensed in UK, other strengths via importation companies and NOT licensed in UK.

Evidence: (2,8,59)

Bisacodyl

Use:

• Constipation

Dose and route:

By mouth:

- **Child 4 years and over**: 5-10mg once daily (recommended to be taken at night), adjust according to response. Increased as necessary up to 20mg daily

By rectum (suppository):

- **Child 2 years and over**: 5-10mg once daily; adjust according to response

Notes:

- Stimulant laxative.

Therapeutics

- Acts by local effect on the colonic mucosa.
- Limited data exist on the safety and efficacy of regular and long term use. Prolonged or excessive use can cause electrolyte disturbance.

Pharmacokinetics

- Onset of action: tablets 10–12 hours, suppositories act in 20–60 min

Administration

- Suppositories must be in direct contact with mucosal wall.
- Enteric coated tablets. Do not crush.
- Not suitable for enteral tube administration.

Available as

- Gastro-resistant tablets (5mg) and suppositories (5mg, 10mg).

Evidence: (1,2,60)

Buprenorphine

Use:

- Moderate to severe pain
- Alternative opioid in patients with end stage (4 or 5) renal failure

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

***Stable* pain in patients already receiving regular strong opioids**

By transdermal patch:

- By titration or convert using oral morphine equivalent (OME) see Appendix 1. Not suitable for dose titration in patients with unstable pain.
- Consider reducing the dose of buprenorphine by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

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

7 day patches

Oral morphine 12mg/24hours	≡	Buprenorphine 5micrograms/hour
Oral morphine 24mg/24hours	≡	Buprenorphine 10micrograms/hour
Oral morphine 36mg/24hours	≡	Buprenorphine 15micrograms/hour
Oral morphine 48mg/24hours	≡	Buprenorphine 20micrograms/hour

3 or 4 day patches

Oral morphine 84mg/24hours	≡	Buprenorphine 35micrograms/hour
Oral morphine 126mg/24hours	≡	Buprenorphine 52.5micrograms/hour
Oral morphine 168mg/24hours	≡	Buprenorphine 70micrograms/hour

Systemic analgesic concentrations are generally reached within 12–24 hours after applying patch, but levels continue to rise for 32–54 hours (pharmacokinetic profile may differ slightly between preparations, check SPC for full details).

If converting from:

- 4-hourly oral morphine: administer regular morphine doses for the first 12 hours after applying the patch.
- 12-hourly slow release morphine: apply the patch and administer the final slow release dose at the same time.
- 24-hourly slow release morphine: apply the patch 12 hours after the final slow release dose.
- Continuous morphine infusion: continue the infusion for 8- 12 hours after applying the patch.

Pain in opioid naive patients

By sublingual route

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child body-weight less than 25kg**: 5micrograms/kg/dose, maximum 100micrograms/dose, every 8 hours (using injection solution)
- **Child body-weight 25–37.5 kg**: 100micrograms every 6-8 hours
- **12 years and over body-weight 40kg and over**: 200micrograms every 6-8 hours

Titrate the dose every 4–5 days, based on analgesic requirements. Typical adult dose 800micrograms–1.2mg/24hours, given as 200–400micrograms every 6-8 hours

By subcutaneous, intramuscular or slow intravenous injection

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child 6 months-11 years**: 3micrograms/kg/dose, maximum 300micrograms, every 6–8 hours.
- **12 years and above**: 300 micrograms every 6–8 hours.

Titrate the dose, based on analgesic requirements up to a typical adult maximum dose of 600mg every 6-8 hours.

Notes:

- Strong opioid with both agonist and antagonist properties.

Licensing

- Sublingual tablets not licensed for use in children < 6 years old. Patches not licensed for use in children.

Therapeutics

- Doses quoted for opioid naive patients reflect the lower end of ranges quoted by manufacturers and BNFc in view of equianalgesic ratios and clinical experience in both adult and paediatric palliative care.
- Ceiling effect for respiratory depression, however life- threatening respiratory depression can still occur.
- Causes less constipation than some other opioids.
- May be particularly beneficial in neuropathic pain and hyperalgesia
- Sublingual administration not appropriate for breakthrough pain due to long duration of action
- Negligible bioavailability if swallowed due to extensive first pass metabolism
- Effects only partially reversed with naloxone at conventional doses. Theoretical risk of withdrawal symptoms, including pain, in children dependant on high doses of other opioids.
- Has been given as continuous intravenous or subcutaneous infusion over 24 hours. Relatively long half-life means that equianalgesic studies based on single doses are likely to under-represent equianalgesia as a continuous infusion
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Caution

- Caution in hepatic impairment.
- Rate of absorption from patch is affected by temperature with risk of accidental overdose including respiratory depression: caution with pyrexia or increased external temperature such as hot baths.
- Remove patches before MRI scanning due to risk of burns.

Side effects

- Patches may cause contact dermatitis. This may be reduced by topical application of budesonide inhaler spray to the area where the patch is to be applied.

Pharmacokinetics

- Clearance may be faster in some children.
- Duration of action in adults 6-8 hours versus 4-5 hours for morphine. Single-dose studies are therefore likely to underestimate the relative equianalgesic ratio of buprenorphine. Opioid potencies should be considered as an approximate guide, particularly for children for whom very little pharmacokinetic data is available. See Appendix 1 for approximate opioid equivalent data

Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit these enzymes including ciprofloxacin, erythromycin, and fluconazole. Levels reduced by drugs that induce these enzymes including carbamazepine and phenobarbital.

Administration

- MHRA advises that *fentanyl* matrix patches must not be cut due to the risk of life threatening and potentially fatal opioid toxicity. Similar considerations would be expected to apply to cutting buprenorphine patches. Buprenorphine patches should therefore not generally be cut. A decision to cut a buprenorphine matrix patch must be made on a case-by-case basis, weighing up the potential risks and benefits. Cut matrix (see Summary of Product Characteristics) patches diagonally if a smaller dose is required. Only matrix patches can be cut.
- For intravenous infusion dilute in sodium chloride 0.9% to a concentration of 15micrograms/ml. For subcutaneous infusion dilute in sodium chloride 0.9%. Limited compatibility data for mixing with other drugs used in palliative care

Available as

- *Tablets* (200micrograms, 400micrograms) for buccal administration. Tablets may be halved. Higher strength sublingual tablets also available but these are indicated as an adjunct in the treatment of opioid dependence. Take care with prescribing.
- *Patches*: several brands (and generics) of transdermal patches with 7 day, 4 day (96 hour) and 3 day (72 hour) release profiles. Patch size expressed in micrograms/hour. Only matrix patches can be cut. Prescribe by brand where possible: caution when switching between formulations.
- *7 day patches*: BuTrans®, Butec®, Bupramyl®, Panitaz®, Reletrans®, Sevodyne®. Available as 5micrograms /hour for 7 day), 10micrograms /hour for 7 days, 15micrograms/hour for 7 day) and 20micrograms/hour for 7 days
- *4 day (96 hour) patches*: Bupeaze®, Buplast®, Relevtec®, TransTec®. Available as 32.5micrograms/hour for 96 hours, 52.5micrograms/hour for 96 hours, and 70micrograms/hour for 96 hours
- *3 day (72 hour) patches*: Hapactasin®-applied every 72 hours. Available as 35micrograms/hour for 72 hours, 52.5micrograms/hour for 72 hours and 70micrograms/hour for 72 hours
- *Injection:* for intravenous or subcutaneous injection solution 300micrograms/ml

CD

- CD Schedule 3 (CD No Register). Local protocols may require safe storage.

Evidence: (1–3,10,61–72)

Carbamazepine

Use:

- Neuropathic pain
- Hyperkinetic movement disorders
- Anticonvulsant

Dose and route:

By mouth:

- **Neonates**: Experience is limited. Initial dose 5mg/kg twice daily
- **Child 1 month-11 years**: Initial dose of 5mg/kg at night or 2.5mg/kg twice daily, increased as necessary by 2.5-5mg/kg every 3–7 days; usual maintenance dose 5mg/kg 2–3 times daily.

  Total daily doses of up to 20mg/kg/day in divided doses have been used
- **12 years and over**: Initial dose of 100–200mg 1–2 times daily; increased slowly to usual maintenance of 200-400mg 2–3 times daily.

  Maximum total daily dose 1.8 g/day in divided doses

By rectum:

- **Child 1 month and over**: Use approximately 25% more than the oral dose, maximum single dose 250mg, up to 4 times daily.

Notes:

Licensing

- Not licensed for use in children with neuropathic pain. Suppositories licensed for short term use only.

Therapeutics

- May cause hyperalgesia on abrupt withdrawal.
- Different preparations may vary in bioavailability: avoid changing formulations or brands.
- Suppositories of 125mg are approximately equivalent to 100mg tablets but final adjustment should always depend on clinical response (plasma concentration monitoring recommended).
- Use ideal body weight (Appendix 7) when calculating doses in obese children

Side effects

- Can cause serious blood, hepatic, and skin disorders. Parents should be taught how to recognise signs of these conditions, particularly leucopoenia.
- Associated with osteopenia and increased risk of fractures. Consider vitamin D supplementation with long term use.
- Neuroleptic malignant syndrome

Interactions

- Induce of cytochrome P450 enzymes CYP2C9 and CYP3A4. Reduces levels of drugs metabolised by these enzymes including alfentanil, amitriptyline, buprenorphine, clobazam, clonazepam, dexamethasone, diazepam, diclofenac, domperidone, erythromycin (erythromycin also increases carbamazepine levels), fentanyl, haloperidol, methadone, midazolam, paracetamol (with increased risk of liver toxicity), risperidone and tramadol. *This list is not exhaustive-seek advice.*

Administration

- Oral liquid has been administered rectally-should be retained for at least 2 hours if possible but may have a laxative effect.
- Use the liquid preparation for administration via an enteral feeding tube. Dilute with equal volume of water to minimise adsorption to the feeding tube immediately prior to administration. There may be some tube resistance but not blockage when administering via enteral feeding tubes due to high viscosity of liquid.
- Doses above 800mg/day may cause bloating due to the sorbitol content of the liquid. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy. An increase in side effects such as dizziness is possible owing to the rapid delivery into the small bowel. Consider decreasing the dose and increasing the dosing frequency if side effects are problematic.

Patient information

- See Medicines for Children leaflet: “Carbamazepine (oral) for preventing seizures” https://www.medicinesforchildren.org.uk/medicines/carbamazepine-oral-for-preventing-seizures/

Available as

- Tablets (100mg, 200mg, 400mg), liquid (100mg/5 ml), suppositories (125mg, 250mg), and modified release tablets (200mg, 400mg).

Evidence: (1,8,73,74)

Celecoxib

Use:

- Pain, inflammatory pain, bone pain, stiffness. Not used first line
- Post-operative pain where other non-steroidal anti-inflammatory drugs (NSAIDS) are contraindicated

Dose and route:

By mouth:

- **Child over 2 years**:

  Body-weight 10-25 kg: 2-3mg/kg/dose twice daily, maximum 50mg twice daily

  Body-weight more than 25 kg: 100mg twice daily

- **Over 16 years**: 100mg twice daily, increased in severe pain to 200mg twice daily

Notes

- Selective cyclo-oxygenase-2 inhibitor.

Licensing

- Not licensed in the UK for use in children.

Therapeutics

- Dose based on management of juvenile rheumatoid arthritis.
- No difference in tolerability or efficacy has been shown between the selective cox-2 inhibitors (etoricoxib, celecoxib) and the non-selective NSAID, naproxen.
- Parecoxib may be an alternative if the enteral route is not available.
- Does not increase bleeding time.

Contraindications, cautions

- Caution in known CYP2C9 slow metabolizers.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

Side effects

- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term.
- All NSAIDs are associated with serious gastro-intestinal toxicity. COX-2 inhibitors are associated with a lower risk of serious upper gastro-intestinal side effects than non-selective NSAIDs. Consider prescription of a proton pump inhibitor with prolonged use. May exacerbate Crohn's disease.

Hepatic impairment, renal impairment

- Caution in renal impairment: avoid in severe renal impairment.
- Caution in hepatic impairment.

Interactions

- Inhibitor of cytochrome P450 enzyme CYP2D6. May increase the plasma concentrations of other drugs metabolized by this enzyme including amitriptyline, ondansetron and oxycodone.
- Metabolised by CYP2C9. Levels increased by drugs that inhibit this enzyme including fluconazole and in known CYP2C9 slow metabolisers. Levels reduced by drugs that induce this enzyme including carbamazepine
- Reduce dose of celecoxib by 50% if administered with fluconazole.

Administration

- Capsules may be opened and contents mixed with soft food immediately before administration. For administration via an enteral feeding tube, the capsule may be opened and the contents mixed with water to form a milky suspension.

Available as

- Capsules 100mg, 200mg. Also available in UK as an unlicensed ‘special’ oral suspension (100mg/5ml Quantum Pharmaceuticals)

Evidence: (2,3,75–79)

Chloral hydrate

Use:

- Seizures in severe epileptic encephalopathy (seek specialist advice)
- Status dystonicus (seek specialist advice)
- Short term (up to 2 weeks) treatment of insomnia in children and young people with suspected or definite neurodevelopmental disorder where other behavioural and pharmacological measures have failed
- Procedural sedation in neonates

Dose and route:

Seizures, status dystonicus, insomnia

By mouth or rectum:

- **Neonate, child 1 month-11 years**: Initial dose of 30mg/kg as a single dose at night. May be increased to 50mg/kg at night or when required up to 6-8 hourly.

  Maximum single dose 1g

- **12 years and over**: Initial dose of 500mg as a single dose at night or when required up to 6-8 hourly. Dose may be increased if necessary to 1-2 g.

  Maximum single dose 2g

Procedural sedation in neonatal intensive care

By mouth or rectum:

- **Neonate:** for sedation for procedures in NICU: 30–50mg/kg 45–60 minutes before procedure; doses up to 100mg/kg may be used with respiratory monitoring.

Notes:

Licensing

- Not licensed for agitation, epilepsy or status dystonicus. Not licensed in infants under 2 years for insomnia. Use for treatment of severe insomnia in children and adolescents restricted by MHRA/CHM (2021) to those with a suspected or definite neurodevelopmental disorder when insomnia is interfering with daily life and other therapies have failed.

Therapeutics

- Use in insomnia only when insomnia is interfering with daily life. Long term use in insomnia only under specialist guidance
- Use in movement disorders or epileptic encephalopathy should be under the supervision of a named consultant with appropriate experience and competency in paediatric neurology, neurodisability or palliative care. The lowest effective dose should be used, at the lowest frequency and for the shortest period possible. The need for on-going use should be regularly reviewed.
- May cause agitation if withdrawn suddenly

- Enteral solution contains propylene glycol which may accumulate to potentially harmful levels with repeated dosing in neonates.

Side effects

- Allergic dermatitis; ataxia; confusion; delirium (more common on abrupt discontinuation); GI disorders
- Carcinogenic at high doses in rodents

Pharmacokinetics

- Accumulates with prolonged use
- Prolonged half-life in neonates.

Hepatic impairment, renal impairment

- Avoid in severe renal or hepatic impairment.

Administration

- By mouth: mix with plenty of juice, water, or milk to reduce gastric irritation and disguise the unpleasant taste. Light-sensitive so needs to be given as soon as it is drawn up.
- For rectal administration use oral solution or suppositories (available from 'specials' manufacturers).
- Chloral hydrate oral solution may be administered via enteral feeding tubes. Dilute with water before administration, ideally to 2 or 3 times the original volume as tolerated, to reduce risk of gastric irritation. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (chloral betaine 707mg = choral hydrate 414mg— Welldorm®), oral solution (143.3mg/5ml, 500mg/5ml). Oral solutions contain propylene glycol. The RCPCH and NPPG recommend that, when a liquid formulation of chloral hydrate is required, 500 mg/5 mL is used.
- Suppositories (available as various strengths 25mg, 50mg, 60mg, 100mg, 200mg, 500mg from 'specials' manufacturers).

Evidence: (2,11,80–85)

Chlorpromazine

Use:

- Hiccup
- Nausea and vomiting in end-of-life care (where other drugs are unsuitable)
- Agitated delirium in end-of-life care

Dose and route:

By mouth:

- **Child 1-5 years**: 500micrograms/kg 6-8 hourly, adjusted according to response, maximum 40mg daily
- **Child 6-11 years**: 10mg 6-8 hourly, adjusted according to response, maximum 75mg daily.
- **12 years and over**: 25mg 6-8 hourly adjusted according to response, maximum 150mg daily

Total daily dose can also be given once daily at night

Notes:

Licensing

- Not licensed in children for intractable hiccup.

Therapeutics

- Can be given rectally at doses of approximately twice those used via oral route

Cautions

- Caution in cardiovascular disease, neurological impairment including CNS depression, epilepsy, myasthenia gravis, severe respiratory disease, blood dyscrasias: monitor blood counts if unexplained infection or fever.

Side effects

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Photosensitisation may occur with higher dosages: avoid direct sunlight.
- Extrapyramidal side effects, neuroleptic malignant syndrome
- Risk of contact sensitisation: tablets should not be crushed; solution should be handled with care.

Hepatic and renal impairment

- Caution in hepatic impairment and jaundice: can precipitate coma.
- Caution in renal impairment: increased cerebral sensitivity. Start with small dose.

Administration

- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets coated (25mg, 50mg, 100mg), oral solution (25mg/5ml, 100mg/5ml). Suppositories from specialist manufacturers

Evidence: (1,2,86–89)

Clobazam

Clo**baz**am has been confused with clo**nazep**am; care must be taken to ensure the correct drug is prescribed, dispensed and administered.

Use:

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

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

By mouth:

- **Child 1 month-5 years**: Initial dose of 125micrograms/kg twice daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 250micrograms/kg twice daily. Maximum 500micrograms/kg, 15mg single dose, twice daily
- **Child 6 years and over**: Initial dose of 5mg daily. Increase every 5 days as necessary and as tolerated to a usual maintenance dose of 300micrograms/kg-1mg/kg daily. Maximum 60mg daily.

  Daily doses of up to 30mg may be given as a single dose at bedtime, higher doses should be divided.

Notes:

Licensing

- Not licensed for use in children less than 6 years of age. Not licensed as monotherapy.

Therapeutics

- Avoid abrupt withdrawal, except when being used for short courses. Caution when changing between different formulations.
- Tolerance in longer term use may be managed by 'switching/rotating' benzodiazepines.

Side effects

- Risk of increased somnolence or sedation when co-administered with cannabidiol, or opiates
- Side effects similar to other benzodiazepines: children are more susceptible to sedation and paradoxical emotional reactions.

Pharmacokinetics, interactions

- Pharmacokinetics influenced by age and co-administration of other medication. Dose adjustment may be needed when co-administered with strong or moderate CYP2C19 inhibitors.

Administration

- Tablets can be administered whole, or crushed and mixed in soft food. The 10mg tablets can be divided into equal halves of 5mg. Clobazam can be given with or without food. Tablets take 1 to 5 minutes to disperse in water. Both oral liquid and tablets dispersed in water may be administered via enteral feeding tubes.

Patient information

- See Medicines for Children leaflet "Clobazam for preventing seizures" https://www.medicinesforchildren.org.uk/medicines/clobazam-for-preventing-seizures/

Available as

- Tablets 10mg, Oral liquid (10mg/5ml, 5mg/5ml-care with differing strengths), capsules and oral suspension available from special manufactures
- Clobazam is not prescribable in NHS primary care except for the treatment of epilepsy; endorse prescription 'SLS'.

CD

- CD Schedule 4, part 1 (CD4-1).

Evidence: (1,90–93)

Clonazepam

Clo**nazep**am has been confused with clo**baz**am; care must be taken to ensure the correct drug is prescribed, dispensed and administered.

Use:

- Tonic-clonic seizures
- Partial seizures
- Cluster seizures
- Myoclonus
- Neuropathic pain
- Restless legs
- Anxiety, including anxiety associated with dyspnoea, panic attacks
- Oral dysaesthesia in the adolescent

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Epilepsy

By mouth

- **Child 1 month-11 months**: Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 500micrograms–1mg at night, or in 2-3 divided doses.
- **Child 1-4 years**: Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 1–3mg at night, or in 2 -3 divided doses.
- **Child 5-11 years**: Initially 500micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6mg at night or in 2 -3 divided doses
- **12 years and over**: Initially 1mg at night for 4 nights, increased over 2–4 weeks to usual maintenance of 4–8mg at night, or in 2-3 divided doses.

  Higher doses may be used in complex seizure disorders under guidance from a paediatric neurologist

Anxiolysis, neuropathic pain, myoclonus and restless legs

By mouth

- **Child 1 month-11 months**: Initially 125micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 250–500micrograms at night, or in 2-3 divided doses.
- **Child 1-4 years**: Initially 125micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 500micrograms-1.5mg at night, or in 2 -3 divided doses.
- **Child 5-11 years**: Initially 250micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 1.5–3mg at night or in 2 -3 divided doses
- **12 years and over**: Initially 500micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 2–4mg at night, or in 2-3 divided doses.

Oral dysaesthesia (burning mouth syndrome)

- Rinse with 100micrograms/ml solution

Notes

Licensing

- Licensed for use in children for status epilepticus and epilepsy. Not licensed for neuropathic pain. Tablets licensed in children. Not licensed in the UK for SC use.

Therapeutics

- Effective anticonvulsant often used as a 3rd line “add-on”.
- Avoid abrupt withdrawal, except when being used for short courses. Caution when changing between different formulations
- Tolerance in longer term use may be managed by ‘switching/rotating’ benzodiazepines.
- Dose may be increased for short periods of 3-5 days during times of increased seizures e.g. from viral illness.
- Approximately 20 times more potent than diazepam as an anxiolytic-sedative. (i.e. 250micrograms clonazepam equivalent to 5mg diazepam orally or 2.5mg IV/SC midazolam). See Appendix 4.
- Has been used as a subcutaneous or intravenous infusion in status epilepticus resistant to other anticonvulsants. However, the injection is no longer available in the UK. Intravenous or subcutaneous doses are approximately equal to oral doses. Due to the long half -life a loading dose should be given in patients not already receiving clonazepam
- Doses of up to 1.4mg/kg/24hours have been used in status epilepticus in PICU environment.

Contraindications, cautions

- Contraindicated in myasthenia gravis.
- Avoid in acute or severe respiratory failure unless imminently dying. Caution in chronic respiratory disease or sleep apnoea.
- Avoid abrupt withdrawal.

Side effects

- Associated with salivary hypersecretion and drooling.

Pharmacokinetics

- Oral biovailability >80%; the same dose can be used when converting from PO to IV or SC routes.
- Long elimination half-life of up to 60 hours. Infusions may take up to 6 days to reach steady state. Risk of accumulation and toxicity. Consider loading dose to reach steady state more quickly.

Hepatic and renal impairment

- Caution in mild or moderate hepatic impairment: avoid in severe hepatic impairment.

Patient information

- See Medicines for Children leaflet: "Clonazepam for preventing seizures" https://www.medicinesforchildren.org.uk/medicines/clonazepam-for-preventing-seizures/

Administration

- Licensed oral liquid formulation contains alcohol. Tablets or other unlicensed non-alcohol-containing liquid preparations are therefore preferred.
- Tablets may be dispersed in water for oral administration or administration via a feeding tube.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Adheres to plastic tubing. Tablets should be dispersed in at least 30ml of water to prevent binding to enteral feeding tubes. Flush enteral feeding tubes well after administration. Use non-PVC tubing for infusions.
- Diluted clonazepam injection is stable for up to 12 hours. Infusions should ideally be changed every 12 rather than every 24 hours.
- Compatible with most drugs commonly administered via continuous subcutaneous infusion via syringe driver. Dilute with water for injection or sodium chloride 0.9%.

Available as

- Tablets (500micrograms scored, 1mg, 2mg scored); liquid (500micrograms in 5ml and 2mg in 5ml now available as licensed preparations from Rosemont, but neither are licensed for use in children due to high alcohol content; other unlicensed oral liquids are available from specials manufacturers); clonazepam drops 2.5mg/ml available from some special manufacturers; injection (1mg/ml unlicensed import).
- The RCPCH and NPPG recommend that, when a liquid special of clonazepam is required, the 2mg/5ml strength is used:

CD

- CD Schedule 4 part 1 (CD4-1).

Evidence: (1,2,11,90,94–96)

Clonidine

Use:

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

Doses and route:

Pain, sedation, opioid sparing, prevention of opioid withdrawal effects, spasticity, movement disorder

By mouth or intravenous bolus:

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

  For long term use consider conversion to a transdermal patch once an effective dose has been established

By transdermal patch

Conversion from oral, intravenous or subcutaneous routes

Clonidine 100-150micrograms/24hours	≡	Clonidine 2.5mg patch (delivers 100micrograms/24hours)
Clonidine 150-250micrograms/24hours	≡	Clonidine 5mg patch (delivers 200micrograms/24hours)
Clonidine 250-350micrograms/24hours	≡	Clonidine 7.5mg patch (delivers 300micrograms/24hours)

If more than 2.5mg patch to be used i.e.200micrograms/24hours, consider using 2 smaller patches to be changed on different days of the week to reduce end of dose effect.

Therapeutic clonidine levels are achieved 2 to 3 days after initial application of patch. Oral, intravenous or subcutaneous clonidine therefore needs to be reduced gradually after applying the patch:

Apply patch on day 1.

Day 1: continue 100% of oral/IV dose

Day 2: reduce to 50% of oral/IV dose

Day 3: reduce to 25% oral/IV dose

Day 4: patient will only need patch

By continuous intravenous or subcutaneous infusion (most experience on PICU)

- **Child over 1 month**: 0.1-2micrograms/kg/hour:
  approximately 2.5-50micrograms/kg/24hours

Usual starting doses:

- **Child less than 6 months**: 0.4micrograms/kg/hour
  approximately 10micrograms/kg/24hours
- **Child 6 months and over**: 0.6micrograms/kg/hour, approximately 14micrograms/kg/24hours

Total daily dose can also be given as subcutaneous injection in two divided doses

Behavioural problems, tics, Tourette's syndrome:

By mouth:

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

  For long term use consider conversion to a transdermal patch (see above) once an effective dose has been established

Anxiety, procedural sedation, autonomic dysreflexia:

By mouth, or buccal/sublingual (using injection solution or oral tablets):

- **Neonate**: 4micrograms/kg as a single dose
- **Child 1 month and over**: 4micrograms/kg as a single dose, maximum 150 micrograms/ dose.

Premedication given 45-60 minutes before procedure

For autonomic dysreflexia a further dose up to 2micrograms/kg can be given after an hour if required

Regional nerve block (specialist use only):

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

Notes

- Mixed alpha-1 and alpha-2 agonist (mainly alpha-2). Appears to have synergistic analgesic effects with opioids and prevents opioid withdrawal symptoms. Also useful for its sedative effect. Use established in ADHD, behavioural problems and tics.

Licensing

- Not licensed for use in children. Patches not licensed in UK. Licensed for the treatment of hypertension.

Therapeutics

- Consider monitoring blood pressure and pulse on starting treatment and after each dose increase.
- Avoid abrupt discontinuation: risk of acute withdrawal symptoms including rebound hypertension.
- Can be administered by the buccal route. Some drug may be swallowed. This is unlikely to significantly affect the bioavailability but may delay the onset of action.
- Can be administered by continuous subcutaneous infusion for status dystonicus.
- Can be used as substitute for tizanidine if enteral route is unavailable due to similar mechanism of action although less hypotensive effect.
- Higher doses up to 200micrograms/kg/24hours via enteral, intravenous and transdermal routes have been reported in status dystonicus although sedation is a significant adverse effect.

Cautions

- Caution in bradycardia, Raynaud's or other occlusive peripheral vascular disease.
- Remove patches before MRI scanning: risk of burns.

Side effects

- Common side effects include constipation, nausea, dry mouth, vomiting, postural hypotension, dizziness, sleep disturbances, headache.

Interactions

- Effects abolished by drugs with alpha-2 antagonistic activity e.g. tricyclics and antipsychotic drugs. Antihypertensive effects may be potentiated by other drugs used to lower blood pressure.

Pharmacokinetics

- Oral, sublingual and rectal bioavailability 75-95%, although this may be lower in children. Generally 1:1 oral:sublingual:IV:SC:PR conversion can be used. Half-life 12-33 hours.
- Anecdotal reports of use of rectal clonidine. Pharmacokinetic studies suggest almost 100% bioavailability via this route. Single rectal doses of 2.5-4micrograms/kg have been used.
- Has also been administered via intranasal route using atomised injection solution using doses similar to oral route. Onset of action is faster than by mouth.
- Onset of action 30-60 minutes via oral, sublingual or rectal routes. Time to peak plasma concentration: oral 1.5-5 hours; epidural 20 minutes; transdermal, continuous intravenous and subcutaneous infusion 2-3 days.
- Considerable inter-individual variation in bioavailability of patches: caution when converting from other routes.

Hepatic impairment, renal impairment

- Accumulates in renal impairment. Consider reducing dose if GFR less than 30ml/min/1.73m^2

Administration

- Oral solution may be administered via an enteral feeding tube. Alternatively, tablets may be crushed and dispersed in water for administration via an enteral feeding tube. The 25microgram tablets do not appear to disperse in water as readily as the 100microgram tablets. IV solution may also be given via the enteral tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Injection can be administered by buccal or sublingual route. Alternatively oral tablets can be administered sublingually
- Rectal administration using parenteral preparation diluted to 10micrograms/ml with sodium chloride 0.9%
- Parenteral solution can be administered undiluted as a subcutaneous injection or diluted in sodium chloride 0.9% for continuous subcutaneous infusion. Can be combined with a number of other drugs commonly administered by continuous subcutaneous infusion in palliative care: consult appropriate specialist texts.

Patient information

- Patient information: see Medicines for Children leaflet: “Clonidine for Tourette’s syndrome ADHD and sleep onset disorder” https://www.medicinesforchildren.org.uk/medicines/clonidine-for-tourettes-syndrome-adhd-and-sleep-onset-disorder/

Available as

- Tablets (25micrograms, 100micrograms), oral solution (50micrograms/5ml), injection (150 micrograms/ml), transdermal patch (available via importation company)
  - 2.5mg patch (=100 micrograms clonidine/day for 7 days)
  - 5mg patch (=200 micrograms clonidine/day for 7 days)
  - 7.5mg patch (= 300 micrograms clonidine/day for 7 days)

Evidence: (3,11,58,81,97–111)

Co-danthramer (dantron and poloxamer 188)

Use:

• Constipation in end-of-life care

Dose and route:

By mouth:

Co-danthramer 25/200 suspension 5ml = one co-danthramer 25/200 capsule (Dantron 25mg, poloxamer ‘188’ 200mg):

- **Child 2-11 years**: 2.5–5ml at night
- **Child 6-11 years**: 1 capsule at night
- **12 years and over**: 5–10ml or 1–2 capsules at night.

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

- **12 years and over**: 5ml or 1–2 capsules at night.

Notes

- Stimulant laxative (dantron) combined with a wetting agent (poloxamer 188)

Licensing

- Licensed for terminally ill patients of all ages

Side effects

- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- Rodent studies indicate potential carcinogenic risk.
- Dantron can turn urine red/brown.

Administration

- Suspension can be used with enteral feeding tubes but is quite viscous, needing some pressure on syringe and to be flushed well after administration. Administration into the jejunum is unlikely to affect pharmacological response.

Available as

- Co-danthramer 25/200 suspension 5 ml = one co-danthramer 25/200 capsule (Dantron 25mg, poloxamer ‘188’ 200mg), Strong co-danthramer 75/1000 suspension 5 ml = two strong co-danthramer 37.5/500 capsules.

Evidence: (1,2)

Co-danthrusate (dantron and docusate sodium)

Use:

- Constipation in end-of-life care

Dose and route:

By mouth:

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

- **Child 6-11 years**: 5ml or 1 capsule at night
- **12 years and over**: 5–15ml or 1–3 capsules at night

Notes

- Stimulant laxative (dantron) combined with a softener (docusate sodium)

Licensing

- Licensed for terminally ill patients of all ages

Therapeutics

- Not recommended for under 6 years.

Side effects

- Avoid prolonged skin contact due to risk of irritation and excoriation (avoid in urinary or faecal incontinence, or children with nappies).
- Dantron can turn urine red/brown.
- Rodent studies indicate potential carcinogenic risk.

Administration

- No specific data on enteral tube administration are available for this preparation. If necessary use the suspension and flush tube well after use. Consider diluting with water to aid administration.

Available as

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

Evidence: (1,2)

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: (1,2,112)

Cyclizine

Use:

- Antiemetic of choice for raised intracranial pressure.
- Nausea and vomiting of vestibular origin or where other antiemetics (metoclopramide, $5HT_3$ antagonists) have failed.

Dose and route:

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

- **Child 1 month- 5 years**: 500micrograms–1mg/kg up to 3 times daily, maximum single dose 25mg
- **Child 6-11 years**: 25mg up to 3 times daily
- **12 years and over**: 50mg up to 3 times daily

By rectum:

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

By continuous intravenous or subcutaneous infusion:

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

Notes:

- Antihistaminic, antimuscarinic antiemetic.

Licensing

- Tablets are not licensed for use in children under 6 years old. Injection is not licensed for use in children.

Therapeutics

- Injection solution has also been given sublingually in adults using same doses as oral or rectal routes.
- Anticholinergic effects reduce effect of prokinetic antiemetics e.g. domperidone, metoclopramide

Contraindications, cautions

- Avoid in severe cardiac failure: may cause fall in cardiac output.
- Increased risk of transient paralysis with intravenous use in patients with neuromuscular disorders.

Side effects

- Antimuscarinic side effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.
- Risk of site reactions when administered via SC or IV route
- Rapid SC or IV bolus can lead to 'light-headedness': disliked by some but enthralling to others leading to repeated requests for IV cyclizine.

Pharmacokinetics

- Some evidence suggests 50% oral bioavailability: consider reducing dose when converting oral to IV or SC routes.
- May accumulate with continued use.

Hepatic impairment, renal impairment

- Avoid in severe liver disease.

Interactions

- Increased sedative and antimuscarinic effect when given with tricyclics, anxiolytics, MAOI's.

Administration

- For continuous subcutaneous or intravenous infusion, dilute only with water for injection or 5% dextrose*: incompatible* with 0.9% sodium chloride causing precipitation.
- Concentration dependent *incompatibility* with alfentanil, dexamethasone, diamorphine and oxycodone.
- Suppositories must be kept refrigerated.
- Tablets may be crushed for oral administration. The tablets do not disperse well in water, but if shaken in 10 ml water for 5 minutes, the resulting dispersion may be administered immediately via an enteral feeding tube. Alternatively use oral suspension. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (50mg), suppositories (12.5mg, 25mg, 50mg, 100mg from 'specials' manufacturers) and injection (50mg/ml). Oral suspension unlicensed special (50mg/5ml Nova Laboratories, 5mg/5ml). Alternative suppliers may also be available.

Evidence: (1,3,8,113)

Dantrolene

Use:

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

Dose and route:

Doses should be increased *slowly*

By mouth:

- **Child 5-11 years**: Initial dose of 500micrograms/kg once daily; increase after 7 days to 500micrograms/kg/dose 3 times daily. Increase every 7 days by a further 500micrograms/kg/dose until response

  Maximum recommended dose 2mg/kg 3–4 times daily, maximum total daily dose 400mg

- **12 years and over:** Initial dose of 25mg once daily; increase after 7 days to 25mg 3 times daily. Increase by a further 500micrograms/kg/dose every 7 days until response.

  Maximum recommended dose 2mg/kg 3–4 times daily, maximum total daily dose 400mg

Notes:

Licensing

- Not licensed for use in children.

Therapeutics

- Acts directly on skeletal muscle so can be used concurrently with baclofen and diazepam.

Contraindications, cautions

- Caution in patients impaired cardiac or pulmonary function.

Side effects

- Risk of hepatotoxicity; consider checking liver function before and at regular intervals during therapy.
- Pericarditis, pleural effusion, respiratory depression, exacerbation of cardiac insufficiency, tachycardia and blood pressure changes, drowsiness, dizziness, weakness, nausea and diarrhoea.

Hepatic impairment, renal impairment

- Contraindicated in hepatic impairment: avoid in liver disease or concomitant use of hepatotoxic drugs.

Administration

- Capsules can be opened and dispersed in water for administration via gastrostomy. Alternatively use oral suspension.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Capsules (25mg, 100mg), oral suspension (extemporaneous formulation 5mg/ml).

Evidence: (1–3,114)

Dexamethasone

Use:

- Headache associated with raised intracranial pressure caused by a tumour
- Malignant spinal cord compression
- Reduction of symptoms due to peri-tumour oedema and inflammation
- Neuropathic pain due to nerve compression
- Bone pain due to malignant infiltration
- Antiemetic either as an adjuvant or in highly emetogenic cytotoxic therapies

Dose and route:

Headache associated with raised intracranial pressure, spinal cord compression

By mouth or short intravenous infusion over 15-20 minutes:

- **Child 1 month- 11 years**: 250micrograms/kg twice daily for 5 days; then stop
- **12 years and over:** 8mg twice daily (or 16mg once daily) for 5 days, then stop

If symptoms recur consider a further pulse of dexamethasone followed by a washout period to reduce side effects. Reduce to the minimum effective dose if discontinuation is not possible.

Prescribe injection or infusion as dexamethasone *base.*

Higher doses may be advised particularly in malignant spinal cord compression.

Once and twice daily doses to be given before midday to reduce likelihood of corticoid induced insomnia

Reduction of symptoms due to peri-tumour oedema and inflammation

Neuropathic pain due to malignant nerve compression

Bone pain due to malignant infiltration

By mouth, short intravenous infusion over 15–20 minutes, or subcutaneous injection

- **Child under 1 year**: Initial dose 250micrograms once or twice daily.
- **1- 5 years**: Initial dose 1mg once or twice daily.
- **6-11 years**: Initial dose 2mg once or twice daily.
- **12 years and over**: 4mg once or twice daily.

Initial therapy for 2–5 days then stop.

If symptoms recur consider a further pulse of dexamethasone followed by a washout period to reduce side effects. Reduce to the minimum effective dose if discontinuation is not possible.

Prescribe injection or infusion as dexamethasone *base.*

Once and twice daily doses to be given before midday to reduce likelihood of corticoid induced insomnia

Antiemetic

By mouth, short intravenous infusion over 15-20 minutes, or subcutaneous injection:

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

Prescribe injection or infusion as dexamethasone *base*.

Notes:

Licensing

- Not licensed for use in children as an anti-emetic.

Therapeutics

- High glucocorticoid activity but relatively insignificant mineralocorticoid activity.
- Dexamethasone 1mg = 7mg prednisolone, anti-inflammatory equivalence.
- Prescribe injection or infusion as dexamethasone *base* i.e. as “dexamethasone”, not “dexamethasone phosphate” or “dexamethasone sodium phosphate”.
- Long duration of action. Can be given in a single daily dose each morning for most indications. Administration of the daily dose of dexamethasone before midday reduces the likelihood of corticosteroid induced insomnia and agitation.
- Adverse effects quickly outweigh the benefits: use short courses wherever possible or reduce as quickly as possible to lowest effective dose.
- Can be stopped abruptly if given for less than two weeks. Doses should be weaned gradually over several weeks for longer courses in order to allow recovery of the hypo-pituitary axis and avoid Addisonian crisis.
- Dexamethasone (base) 1mg = dexamethasone phosphate 1.2mg = dexamethasone sodium phosphate 1.3mg.

Side effects

- Rapid injection can cause paraesthesia and cardiovascular collapse.
- Problems of body-weight gain and Cushingoid appearance are major concerns specifically in children.
- Other side effects include: diabetes, hypertension, osteoporosis, muscle wasting, peptic ulceration and behavioural problems and agitation, also extreme exacerbation of and lability of mood (tearfulness, physical aggression), hypokalaemia.
- Consider the use of proton pump inhibitor (PPI) to prevent gastrointestinal irritation.
- Some injection formulations may contain latex: consult SPC.

Pharmacokinetics

- Oral bioavailability >80%; 1:1 oral:IV:SC conversion can be used.

Interactions

- Moderate inducer of cytochrome P450 enzyme CP3A4. May reduce levels of drugs that are metabolised by this enzyme.
- Also metabolised by CYP3A. Levels increased by drugs that inhibit this enzyme including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine and phenobarbital.

Administration

- Tablets may be dispersed in water if oral liquid unavailable. Oral solution or tablets dispersed in water may be administered via an enteral feeding tube.
- Alkaline drug: increased risk of precipitation when used in combination with other drugs in a syringe driver.

Patient information

- See Medicines for Children Leaflet “Dexamethasone for croup” https://www.medicinesforchildren.org.uk/medicines/dexamethasone-for-croup/

Available as

- Tablets (500 micrograms, 2mg, 4mg), soluble tablets (2mg, 4mg, 8mg, 10mg, 20mg) oral solution (2mg/5ml 10mg/5ml and 20mg/5ml) and injection dexamethasone base 3.8mg/ml and 3.3mg/ml.

Evidence: (2,3,10)

Diamorphine

Use:

- Moderate to severe pain
- Breakthrough pain where oral route is not available, or rapid onset of action is required
- Dyspnoea
- Alternative opioid where large doses need to be administered in small volume

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in patients already receiving regular strong opioids

By continuous subcutaneous or intravenous infusion

Calculate dose of diamorphine by using oral morphine equivalent (OME) from previous analgesia (See table Appendix 1).

Approximate equianalgesic ratios for oral and intravenous morphine and diamorphine

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Diamorphine CSCI or CIVI	6:1	Divide 24hour morphine dose by 6	Morphine oral 30mg/24hours ÷ 6 = diamorphine CSCI 5mg/24hours
Morphine CSCI or CIVI	Diamorphine CSCI or CIVI	2:1	Divide 24hour morphine dose by 2	Morphine CSCI 20mg/24hours ÷ 2 = diamorphine CSCI 10mg/24hours

Breakthrough pain in patients already receiving opioids

Review background analgesia if breakthrough analgesia is required more than twice in a 24-hour period.

By subcutaneous or intravenous routes

- 1/10 to 1/6 (10-16%) of 24-hour diamorphine infusion every 1-4 hours as needed.

By intranasal or buccal route

Approximate equianalgesic ratios for intranasal or buccal diamorphine

Conversion		**Ratio**	**Calculation**	**Example**
From	**To**			
Diamorphine CIVI or CSCI	Intranasal or buccal diamorphine	**1:2**	***Multiply*** 24hour diamorphine dose by 2 *Then* administer 1/10-1/6 every 1- 4 hours as needed	Diamorphine 20mg/24hours x 2 = 40 40 ÷ 10 = 4 40 ÷ 6 = 6.6 Breakthrough dose = 4-6.6mg intranasal diamorphine
Oral morphine	Intranasal or buccal diamorphine	3:1	Divide 24hour morphine dose by 3 *Then* administer 1/10-1/6 every 1- 4 hours as needed	Morphine oral 30mg/24hours ÷ 3 = 10 10 ÷ 10 = 1 10 ÷ 6 = 1.7 Breakthrough dose = 1-1.7mg intranasal diamorphine
Morphine CIVI or CSCI	Intranasal or buccal diamorphine	1:1	Administer 1/10-1/6 24hour morphine dose every 1- 4 hours as needed	Morphine CIVI 60mg/24hours 60 ÷ 10 = 6 60 ÷ 6 = 10 Breakthrough dose = 6-10mg intranasal diamorphine

Pain in opioid naive patients

Doses refer to ***starting*** doses only[a]

Age range	Intranasal or buccal	Intravenous or subcutaneous bolus	Intravenous or subcutaneous infusion/24hours
Neonate	40micrograms/kg/dose 6 hourly	20micrograms/kg/dose 6 hourly	80micrograms/kg/24hours
1- 2 months	60micrograms/kg/dose 6 hourly	30micrograms/kg/dose 6 hourly	120micrograms/kg/24hours
3- 5 months	60micrograms/kg/dose 4 hourly	30micrograms/kg/dose 4 hourly	180micrograms/kg/24hours
6- 23 months	80micrograms/kg/dose 4 hourly	40micrograms/kg/dose 4 hourly	240micrograms/kg/24hours
2-11 years	80-100micrograms/kg maximum 5mg/dose 4 hourly	40micrograms/kg maximum 2.5mg/dose 4 hourly	240-300micrograms/kg/24hours maximum 10mg/24hours
12 years and over	80-100micrograms/kg maximum 5mg/dose 4 hourly	40-50micrograms/kg/dose 4 hourly maximum 2.5mg/dose *Alternatively* 1.25-2.5mg/dose	240micrograms/kg/24hours maximum 15mg/24hours

Injection solution can be used by intranasal or buccal routes. A Mucosal Atomiser Device (MAD) can be used for accuracy of administration.

Dyspnoea

By buccal, intranasal, subcutaneous or intravenous routes

- **Child 1 month and over:** 25-50% of pain doses

Notes:

- Pro-drug of morphine.

Licensing

- Licensed for the treatment of children who are terminally ill.

Therapeutics

- Morphine is normally considered strong opiate of first choice by mouth and for intravenous infusion or continuous subcutaneous infusion. Only benefit of diamorphine via these routes is greater solubility when high doses are required.
- Has been used via intravesical route for bladder spasms and topically in Intra-Site gel for painful skin ulcers (unlicensed indications).

[a] Doses adapted from BNFC ensuring age bands and dosing intervals are consistent, including extrapolating from morphine, taking into account longer half-life in neonates and infants, bio-availability via different routes, and ensuring consistent total daily dose across each age band

- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Pharmacokinetics

- No data directly comparing intranasal with buccal route in children. Bioavailability may be lower for buccal administration particularly if larger volumes are used for administration and some of the drug is swallowed.
- Bioavailability may be affected by developmental changes in nasal anatomy in the neonatal period and infancy

Hepatic impairment, renal impairment

- Increase dosing interval, reduce dose and administer as required rather than regularly in renal impairment. Avoid in severe renal impairment.
- Caution in hepatic impairment: consider reducing dose.

Administration

- Injection powder can be diluted in water for injection for intranasal or buccal administration (unlicensed route of administration).
- Can be given by subcutaneous infusion up to a concentration of 250mg/ml. Dilute with water for injections for CSCI: concentration-related incompatibility with 0.9% sodium chloride at concentrations above 40mg/ml.

Available as

- Injection (5mg, 10mg, 30mg, 100mg, 500mg ampoules). Supplies may be limited

CD

- CD Schedule 2.

Evidence: (1–3,115–121)

Diazepam

Use:

- Anxiety, including anxiety associated with dyspnoea, panic attacks
- Agitation
- Relief of muscle spasm or dystonia
- Status epilepticus

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Short term anxiety relief, panic attacks and agitation

By mouth:

- **Child 2-11 years**: 500micrograms-2mg 3 times daily
- **12 years and over**: Initial dose of 2mg 3 times daily increasing as necessary and as tolerated to a maximum of 10mg 3 times daily.

Relief of muscle spasm, dystonia (as rescue or short-term therapy)

By mouth:

- **Child 1-11 months**: Initial dose of 250micrograms/kg twice daily
- **1-4 years**: Initial dose of 2.5mg twice daily
- **5-11 years**: Initial dose of 5mg twice daily
- **12 years and over:** Initial dose of 10mg twice daily; maximum total daily dose 40mg.

Status epilepticus

By intravenous injection over 3–5minutes:

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

By rectum (rectal solution):

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

Notes

Licensing

- Rectal tubes not licensed for children under 1 year old.

Contraindications, cautions

- Avoid in acute or severe respiratory insufficiency unless in the imminently dying.
- Caution in muscle weakness, respiratory depression, or sleep apnoea.

Side effects

- Dose-dependent drowsiness and impaired psychomotor and cognitive skills.

Pharmacokinetics

- Almost 100% bioavailable when given orally or by rectal solution.
- Onset of action: approximately 15 minutes given orally and within 1-5 minutes given intravenously. Given as rectal solution, diazepam is rapidly absorbed from the rectal mucosa with maximum serum concentration reached within 17 minutes.
- Long plasma half-life of 24-48 hours. The active metabolite, nordiazepam, has a plasma half-life of 48-120 hours.

Hepatic impairment, renal impairment

- Caution in hepatic impairment

Interactions

- Metabolised by cytochrome P450 enzymes CYP2C19 and CYP3A4. Levels increased by drugs that inhibit these enzymes including erythromycin, fluconazole, fluoxetine, and omeprazole. Levels decreased by drugs that induce these enzymes including carbamazepine and phenobarbital.
- Risk of enhanced CNS depressant effect if co-administered with other CNS depressants including neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates or sedative antihistamines.

Administration

- The oral solution may be administered via a gastrostomy tube. Dilute with water before administration to reduce viscosity. For administration via a jejunostomy tube, consider using tablets dispersed in water to reduce osmolarity.

Patient information

- See Medicines for Children leaflet "Diazepam for muscle spasm." https://www.medicinesforchildren.org.uk/medicines/diazepam-for-muscle-spasm/ and "Diazepam (rectal) for stopping seizures" https://www.medicinesforchildren.org.uk/medicines/diazepam-rectal-for-stopping-seizures/

Available as

- Tablets (2mg, 5mg, 10mg), oral solution/suspension (2mg/5ml, 5mg/5ml), rectal tubes (5mg, 10mg), and injection (5mg/ml solution and 5mg/ml emulsion)

CD

- CD Schedule 4 part 1

Evidence: (1,2,8,58,117,122)

Diclofenac Sodium

Use:

- Mild to moderate pain and inflammation
- Musculoskeletal pain

Dose and route:

By mouth or rectum:

- **Child 6 months and over** : Initial dose of 300microgram/kg 3 times daily increasing if necessary to a maximum of 1mg/kg 3 times daily (maximum 50mg single dose).

By intermittent intramuscular injection or intravenous infusion (using Voltarol® injection):

- **Child 2 years and over**: 300-500microgram/kg 1-2 times daily

  Increase, if required, to maximum 1mg/kg 1–2 times daily or 150mg/day, for a maximum of 2 days (see notes below)

Notes:

- Peripheral and central preferential COX 2 inhibitor

Licensing

- Not licensed for use in children under 1 year; suppositories not licensed for use in children under 6 years (except for use in children over 1 year for juvenile idiopathic arthritis); solid dose forms containing more than 25mg not licensed for use in children; injection licensed for short term use (up to 2 days) in adults only

Therapeutics

- Maximum intravenous and intramuscular doses quoted above refer primarily to short term use in post-operative pain. Use lower doses if longer term parenteral use is required.
- Higher doses may have a ceiling effect risking increased adverse effects, particularly with longer term use, without additional analgesic effect.

Contraindications, cautions

- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

Side effects

- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.

- All NSAIDs are associated with serious gastro-intestinal toxicity. Diclofenac is associated with an intermediate risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.

Pharmacokinetics

- Oral bioavailability approximately 30-50%, rectal bioavailability approximately 50%

Interactions

- Metabolised by cytochrome P450 enzyme CYP2C9. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine

Administration

- Smallest dose that can be given practically by rectal route is 3.125mg by cutting a 12.5mg suppository into quarters.
- The Palliative Care Formulary describes unlicensed CSCI use at 50% oral dose, with 0.9% sodium chloride as diluent.
- For IV infusion, dilute with 100-500ml of sodium chloride 0.9% or glucose 5%. Buffer the diluent with sodium bicarbonate (0.5ml of 8.4% or 1ml of 4.2%). Administer over 30 minutes-2 hours.
- Use oral suspension for administration via a feeding tube. There should be no reduction in bioavailability from jejunal administration.

Patient information

- See Medicines for Children leaflet “Diclofenac for pain and inflammation” https://www.medicinesforchildren.org.uk/medicines/diclofenac-for-pain-and-inflammation/

Available as

- Gastro-resistant tablets (25mg, 50mg), modified-release tablets (25mg, 50mg, and 75mg), modified release capsules (75mg and 100mg), injection (25mg/ml Voltarol® , licensed in adults for IV ***infusion*** and IM bolus only, and 75mg/ml Akis®, licensed in adults for IV, IM or SC ***bolus*** only), and suppositories (12.5mg, 25mg, 50mg and 100mg). Oral suspension 50mg in 5ml available as an unlicensed ’special’

Evidence: (1,3,8,123–126)

Dihydrocodeine

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

Evidence: (1–3,127)

Docusate

Use:

- Constipation

Dose and route

By mouth:

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

By rectum:

- **12 years and over**: 1 enema (120mg) as single dose

Notes:

Emulsifying, wetting and mild stimulant laxative

Licensing

- Adult oral solution and capsules not licensed in children < 12 years.

Therapeutics

- Generally a more powerful stimulant laxative than docusate is required for opioid induced constipation
- Oral preparations act within 1–2 days.
- Rectal preparations act within 20mins and may cause a mild localised ‘burning’ sensation.
- Recommended doses may be exceeded on specialist advice.

Administration

- For administration by mouth, solution may be mixed with milk or squash to disguise the unpleasant taste. Oral solution may be administered via an enteral feeding tube. Administration directly into the jejunum will not affect the pharmacological response.

Available as

- Capsules (100mg), oral solution (12.5mg/5ml paediatric, 50mg/5ml adult, 100mg/5ml adult), and enema (120mg in 10g single dose pack).

Evidence: (1–3)

Domperidone

Use:

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

Important safety information

MHRA/CHM advice (updated December 2019): Domperidone for nausea and vomiting: lack of efficacy in children; reminder of contraindications in adults and adolescents

Domperidone is no longer indicated for the relief of nausea and vomiting in children aged under 12 years or those weighing less than 35 kg. A European review concluded that domperidone is not as effective in this population as previously thought and alternative treatments should be considered. Healthcare professionals are advised to adhere to the licensed dose and to use the lowest effective dose for the shortest possible duration (max. treatment duration should not usually exceed 1 week).

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

- Use the minimum effective dose.
- Avoid in known cardiac problems or other risk factors.
- Consider monitoring QTc before initiating treatment and with dose increases

Dose and route

By mouth:

- **Neonate**: 250micrograms/kg 3 times daily. Increase if necessary to 400micrograms/kg 3 times daily
- **Child over 1 month- 11 years**: Initial dose of 250micrograms/kg, maximum 10mg/dose, 3 times daily. Dose may be increased if necessary to 400micrograms/kg 3-4 times daily, maximum 80mg in 24 hours
- **12 years and over**: Initial dose of 10mg 3–4 times daily before food. Dose may be increased, if necessary, to 20mg 3-4 times daily, maximum 80mg in 24 hours.

Notes

Licensing

- Not licensed for use in gastro-intestinal stasis, not licensed for use in children for gastro-oesophageal reflux disease.

Therapeutics

- Reduced ability to cross blood brain barrier: less likely to cause extrapyramidal side effects compared with metoclopramide.
- Promotes gastrointestinal motility: diarrhoea can be an unwanted (or useful) side effect.
- Doses quoted reflect previously authorised maximum doses. Authorised doses have been since reduced due to concern regarding possible cardiac adverse effects. However benefits of higher doses may outweigh the risks in refractory symptoms in paediatric palliative care where safer alternative prokinetics are not available, and risk of cardiac adverse effects is relatively low.
- Prokinetic effect may be reduced by anticholinergic drugs including antiemetics e.g. cyclizine

Contraindications, cautions

- Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Contraindicated in cardiac disease and in conditions where cardiac conduction is, or could be, impaired

Side effects

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended.

Hepatic impairment, renal impairment

- Avoid in hepatic impairment.

Interactions

- Avoid in patients receiving other medications known to prolong QT-interval (e.g. erythromycin, ketoconazole).
- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including erythromycin and fluconazole.

Patient information:

- See Medicines for Children leaflet: “Domperidone for gastro-oesophageal reflux” https://www.medicinesforchildren.org.uk/medicines/domperidone-for-gastro-oesophageal-reflux/

Administration

For administration via an enteral feeding tube: use the suspension formulation, although the total daily dose of sorbitol should be considered. If administering into the jejunum, dilute the suspension with at least an equal volume of water immediately prior to administration.

Available as

- Tablets (10mg), oral suspension (5mg/5 ml).

Evidence: (1,3,8,11,128,129)

Erythromycin

Use:

- Antibiotic typically used in respiratory tract infections, and skin infections
- Gastrointestinal stasis (motilin receptor agonist) is the main indication in palliative care

Dose and route:

Antibiotic

By mouth

- **Neonate**: 12.5mg/kg every 6 hours.
- **Child 1-23 months**: 125mg 4 times daily, increased to 250mg 4 times daily in severe infections. Total daily dose may be given in two divided doses
- **2-7 years**: 250mg 4 times daily, increased to 500mg 4 times daily in severe infections. Total daily dose may be given in two divided doses
- **8 years and over:** 250–500mg 4 times daily, increased to 500mg–1g 4 times daily in severe infections. Total daily dose may be given in two divided doses

By intravenous infusion

- **Neonate**: 10–12.5mg/kg every 6 hours
- **Child 1 month-11 years**: 12.5mg/kg, maximum 1g, every 6 hours
- **12 years and over**: 6.25mg/kg every 6 hours, for mild infections when oral treatment not possible, increased to 12.5mg/kg, maximum 1g, every 6 hours in severe infections

Prokinetic

By mouth or intravenous infusion

- **Neonate, child**: 3 mg/kg 4 times a day

  Benefit is often seen at lower doses. Increase if necessary and as tolerated to a maximum of 1g 4 times daily

Notes:

Licensing

- Not licensed for use in children with gastrointestinal stasis

Contraindications, cautions

- Contraindicated in patients with known clostridium difficile colonisation
- Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval

- Prokinetic effect may be reduced by anticholinergic drugs including antiemetics e.g. cyclizine

Side effects

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in hepatic impairment or co-administration of potentially hepatotoxic drugs
- Associated with increased risk of hypertrophic pyloric stenosis in neonates and infants
- Risk of tachyphylaxis: start at lower doses where possible
- Increased risk of antibiotic associated colitis

Interactions

- Inhibitor of cytochrome P450 enzyme CYP3A4. Increases levels of drugs that are metabolised by this enzyme including alfentanil, buprenorphine, carbamazepine (also reducing erythromycin levels), dexamethasone, diazepam, domperidone, fentanyl and midazolam. This list is not exhaustive-seek advice.
- Also metabolised by CYP3A4. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine (also increasing carbamazepine levels).

Administration

- Dilute the suspension with an equal volume of water before administration via enteral feeding tubes. Absorbed in small intestine

Patient information

- See Medicines for Children leaflet “Erythromycin for treating bacterial infections https://www.medicinesforchildren.org.uk/medicines/erythromycin-for-bacterial-infections/

Available as

- Tablets (250mg, 500mg) and gastro-resistant tablets (250mg, 500mg) and oral suspension (125mg/5ml, 250mg/5ml, 500mg/5ml). Also available as 1g powder for solution for infusion.

Evidence: (1–3,130,131)

Etoricoxib

Use:

- Anti-inflammatory analgesic
- Musculoskeletal pain

Dose and route:

By mouth:

- **Child 12-15 years**: Initial dose of 30mg once daily. Increased as necessary and as tolerated to a maximum of 60mg once daily
- **16 years and over**: Usual dose of 30-60mg once daily. Doses of 90mg daily may be used on a short term basis.

Notes:

- Oral selective cyclo-oxygenase (COX-2) inhibitor.

Licensing

- Not licensed for use in children less than 16 years of age. No pharmacokinetic data in children less than 12 years of age

Therapeutics

- No difference in tolerability or efficacy has been shown between the selective cox-2 inhibitors (etoricoxib, celecoxib) and the non-selective NSAID, naproxen.
- Doses up to 120mg have been used on a short term basis in acute gouty arthritis in adults.

Contraindications, cautions

- All NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID. Etoricoxib may be better tolerated than other NSAIDs in patients with known hypersensitivity.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

Side effects

- All NSAIDs are associated with serious gastro-intestinal toxicity. Etoricoxib is associated with low risk of gastro-intestinal toxicity . Consider prescription of a proton pump inhibitor with prolonged use.
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.
- Common adverse events (1-10% patients): alveolar osteitis; oedema/fluid retention; dizziness, headache; palpitations, arrhythmia; hypertension; bronchospasm; abdominal pain; constipation, flatulence, gastritis, heartburn/acid reflux, diarrhoea, dyspepsia/epigastric discomfort, nausea,

vomiting, oesophagitis, oral ulcer; increased hepatic transaminases (ALT, AST); ecchymosis; asthenia/fatigue, flu-like disease.

Hepatic and renal impairment

- Contraindicated in severe hepatic and severe renal impairment

Interactions

- Potential drug interactions include warfarin (increase in INR); diuretics, ACE inhibitors and angiotensin II antagonists (increased risk of compromised renal function). Etoricoxib does NOT appear to inhibit or induce CYP enzymes. However, the main pathway of etoricoxib metabolism is dependent on CYP enzymes (primarily CYP3A4) so co-administration with drugs that are inducers or inhibitors of this pathway may affect the metabolism of etoricoxib.

Administration

- Etoricoxib tablets may be dispersed in 10ml water and will disintegrate to give fine granules that settle quickly but disperse easily and flush down an 8Fr NG or gastrostomy tube without blockage. Particles of the film coat may remain; flush well. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Film coated tablets 30mg, 60mg, 90mg, 120mg.

Evidence: (1,2,132)

Famotidine (NEW)

Use:

- Histamine H2 antagonist to inhibit / reduce gastric acid secretion
- Episodic dyspepsia
- Gastro-oesophageal reflux disease
- Prevention and treatment of peptic ulceration

Dose and route:

By mouth

Gastro-oesophageal reflux disease

- **Neonate-3 months**: 500micrograms/kg/dose once daily, increased to 1mg/kg/dose once daily if necessary
- **Child 3 months and older**: initial dose 500micrograms/kg/dose twice daily, increasing to 1mg/kg/dose twice daily if required, maximum single dose 40mg

Peptic Ulceration

- **Child 1 year and older**: 500micrograms/kg once daily at night or in 2 divided doses, maximum 40mg/day

Notes:

- Histamine H2 antagonist, reduces gastric acid secretion.

Licensing

- Not licensed for use in children in the UK. Licensed for all ages for gastro-oesophageal reflux disease, and from 1 year of age for peptic ulcer disease in the USA. Limited information of use in neonates.

Therapeutics

- No prokinetic effect, unlike ranitidine

Caution

- Increased incidence of NEC in neonates, especially very low birthweight.
- Use of gastric acid inhibitors, including proton pump inhibitors and H2 blockers, has been associated with an increased risk for development of acute gastroenteritis and community-acquired pneumonia.
- Consider monitoring blood counts and liver function in long term use.
- Continue treatment for some time after symptom relief in peptic ulcer disease.

Side effects

- Constipation; diarrhoea; dizziness; fatigue; headache; myalgia; skin reactions; confusion; agitation; decreased appetite; dry mouth; taste altered; vomiting.

Renal Impairment

- Reduce dose by 50% in severe renal impairment.

Pharmacokinetics

- Duration of effect: 10-12 hours, oral bioavailability: 40-50%.

Drug Interactions

- No clinically important pharmacokinetic drug interactions.
- Increase in gastric pH may decrease the bioavailability of certain drugs (e.g. ketoconazole, itraconazole).
- Concomitant use of antacids or sucralfate may reduce absorption of famotidine: administer antacids at least an hour and sucralfate at least 2 hours after famotidine.

Administration

- Oral: Tablets may be taken with or without food. Tablets can be crushed and mixed with water to aid oral administration (off-label). Without crushing famotidine tablets will disperse in two to five minutes.
- Enteral Feeding Tube: There is no information on administration of famotidine tablets or suspension via an enteral feeding tube. Use of suspension likely to be preferable. Consider dilution if necessary to reduce viscosity and aid administration.
- Injection (available in the USA) can be given intravenously as a slow bolus or short infusion. Has also been given as a subcutaneous bolus or continuous subcutaneous infusion.
- Single case series reporting rectal administration at a dose of 1mg/kg.

Available as

- UK: 20mg and 40mg film-coated tablets, a suspension may be available from UK ‘specials’ manufacturers; extemporaneous formulation for oral suspension available.
- US (available for importation): 10mg, 20mg and 40mg film-coated tablets and oro-dispersible wafers; 40mg in 5ml oral suspension; 10mg/ml injection concentrate.

Evidence (133–146)

Fentanyl

Use:

- Moderate to severe pain
- Transdermal fentanyl should NOT be used in opioid naive patients

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Stable Pain in patients already receiving regular strong opioids

By transdermal patch

Important safety information

MHRA/CHM advice: Transdermal fentanyl patches for non-cancer pain: do not use in opioid naive patients (September 2020)

Fentanyl is a potent opioid: a 12 micrograms per hour fentanyl patch equates to daily doses of oral morphine of approximately 30mg daily

Do NOT use fentanyl patches in opioid naive patients

Use other analgesics and other opioid medicines (opioids) for non-cancer pain before prescribing fentanyl patches

If prescribing fentanyl patches, remind patients or their carers of the importance of:

- Not exceeding the prescribed dose
- Following the correct frequency of patch application, avoiding touching the adhesive side of patches, and washing hands after application
- Not cutting patches and avoiding exposure of patches to heat including via hot water (bath, shower)
- Ensuring that old patches are removed before applying a new one
- Following instructions for safe storage and properly disposing of used patches or patches that are not needed. It is particularly important to keep patches out of sight and reach of children at all times
- Make patients and caregivers aware of the signs and symptoms of fentanyl overdose and advise them to seek medical attention immediately (by dialling 999 and requesting an ambulance) if overdose is suspected
- Remind patients that long-term use of opioids in non-cancer pain (longer than 3 months) carries an increased risk of dependence and addiction, even at therapeutic doses (see Drug Safety Update on risk of dependence and addiction with opioids); before starting treatment with opioids, agree with the patient a treatment strategy and plan for end of treatment

Report suspected adverse drug reactions, including dependence, accidental exposure, or overdose associated with fentanyl patches, via the Yellow Card scheme

Convert using oral morphine equivalent (OME) from previous opioid analgesia see Appendix 1. NOT to be used in opioid naive patients. Not suitable for dose titration in patients with unstable pain.

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

Oral morphine 30mg/24hours	≡	Fentanyl 12micrograms/hour
Oral morphine 60mg/24hours	≡	Fentanyl 25micrograms/hour
Oral morphine 120mg/24hours	≡	Fentanyl 50micrograms/hour
Oral morphine 180mg/24hours	≡	Fentanyl 75micrograms/hour
Oral morphine 240mg/24hours	≡	Fentanyl 100micrograms/hour

Consider reducing the dose of fentanyl by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

Systemic analgesic concentrations are generally reached within 12–24 hours after applying the first patch. If converting from:

- 4-hourly oral morphine: administer regular morphine doses for the first 12 hours after applying the patch.
- 12-hourly slow release morphine: apply the patch and administer the final slow release dose at the same time.
- 24-hourly slow release morphine: apply the patch 12 hours after the final slow release dose.
- Continuous morphine infusion: continue the infusion for 8- 12 hours after applying the patch.

Pain in patients already receiving regular strong opioids

By continuous intravenous or subcutaneous infusion

Convert using oral morphine equivalent (OME) from previous opioid analgesia, see Appendix 1

Conversion		**Ratio**	**Calculation**	**Example**
From	**To**			
Morphine oral	Fentanyl CSCI or CIVI	100:1	Divide 24hour morphine dose by 100 to give fentanyl dose in *mg/24hours* *Then* multiply fentanyl dose in mg/24hours by 1000 to convert to *micrograms/24hours*	Morphine oral 60mg/24hours ÷ 100 = 0.6mg/24hours CIVI fentanyl Fentanyl 0.6mg/24hours x 1000 = 600micrograms/24hours

Consider reducing the dose of fentanyl by 25-50% when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

Breakthrough Pain in patients already receiving regular strong opioids

By buccal or intranasal administration of injection solution

- 1/10 to 1/6 of the total CSCI or CIVI dose as required, up to hourly

  There is no direct correlation between the effective PRN dose and the regular background dose: start with low dose and titrate according to response

  Maximum dose limited to 50micrograms/1ml via the intranasal route and 100micrograms/2ml via buccal route due to available concentration of injection solution (50micrograms/ml).

  Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

By oromucosal application (lozenge with oromucosal applicator), buccal lozenge, buccal tablet, commercially manufactured intranasal spray

- Dose must be titrated against patient's pain. Consult product literature.

  Unlikely to be appropriate for patients receiving less than 60mg oral morphine or oral morphine equivalent per 24 hours

Pain in opioid naive patients

By continuous intravenous or subcutaneous infusion

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate-11months**: 0.15-0.5micrograms/kg/hour (= 3.6-12micrograms/kg/24hours)
- **Child 1 year and over**: 0.25-1micrograms/kg/hour, maximum 50micrograms/hour (6-24micrograms/kg/24hours, maximum 1.2mg/24hours)

By buccal or intranasal administration of injection solution

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate- 11 months**: 1microgram/kg as a single dose
- **Child 2 years and over**: 1-2micrograms/kg as a single dose, with initial maximum single dose of 50micrograms

Maximum dose limited to 50micrograms/1ml via the intranasal route and 100micrograms/2ml via buccal route due to available concentration of injection solution (50micrograms/ml).

By intermittent intravenous or subcutaneous injection

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Neonate- 11 months**: 0.15-0.25micrograms/kg/dose slowly over 3-5 minutes; repeated up to every 30-60 minutes
- **Child over 1 year**: 0.25–0.5micrograms/kg/dose, slowly over 3-5 minutes, repeated up to every 30-60 minutes
- **Adult** initial stat dose of 50–200micrograms, and subsequently 50micrograms, repeated up to every 30-60 minutes

Notes:

- Synthetic opioid, very different in structure from morphine, and therefore ideal for opioid switching.

Licensing

- Injection not licensed for use in children less than 2 years of age. Lozenges and nasal sprays are not licensed for use in children.

Therapeutics

- Evidence that it is less constipating than morphine has not been confirmed in more recent studies
- Buccal, intranasal and oral-transmucosal routes: onset of action 10-15 minutes and duration of action 1-2 hours depending on route and formulation. Therefore suitable for management of breakthrough pain but not ideal for titration of analgesic requirements in unstable pain.
- Some patients experience withdrawal symptoms when changed from oral morphine to transdermal fentanyl, despite adequate pain relief, due to the different mu receptor impact of the two drugs. If this occurs, small rescue doses of morphine can be used and weaned off slowly
- Intranasal administration has been reported for the treatment of dyspnoea in children
- Use adjusted body weight (Appendix 7) to calculate doses in obese children
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Contraindications, cautions

- The MHRA, CQC, and NHS England recommend NOT using transdermal fentanyl in opioid-naive patients due to numerous reports of respiratory depression.
- Greater risk of addiction, tolerance and drug seeking behaviour particularly when administered via buccal or intranasal routes, compared with longer acting opioids.

Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including fluconazole. Levels reduced by drugs that induce this enzyme including carbamazepine and phenobarbital.
- Fentanyl has been reported to reduce the metabolism of IV midazolam**,** reducing the clearance by 30% and extending the half-life by 50%

Hepatic and renal impairment

- Can be safely used in poor, deteriorating or absent renal function.
- Caution in hepatic impairment: Risk of accumulation. Consider dose reduction. May be safer than other opioids in hepatic failure and hepato-renal syndrome.

Patient information

- See Medicines for Children Leaflets "Fentanyl lozenges for pain" https://www.medicinesforchildren.org.uk/medicines/fentanyl-lozenges-for-pain/ and "Fentanyl patches for pain" https://www.medicinesforchildren.org.uk/medicines/fentanyl-patches-for-pain/

Administration

Intranasal

- Intranasal onset of action and duration of action are shorter than oromucosal
- Not always practical and/or well tolerated in children despite favourable pharmacokinetics.
- Intranasal route has also been used for management of respiratory distress in paediatric palliative care.
- For doses less than 50micrograms, the injection solution can be administered by the intranasal route either drop-wise (may be unpleasant) or using a mucosal atomiser device.

Lozenges, buccal / sublingual tablets

- Fentanyl products for the treatment of breakthrough pain are not interchangeable. If patients are switched from another fentanyl containing product a new dose titration is required.
- Oral transmucosal fentanyl accumulates with repeated dosing
- Usefulness of lozenges and buccal / sublingual tablets in children is limited by the dose availability, no reliable conversion factor and requirement for individual dose titration.
- Oral transmucosal products are not suitable for opioid naive patients. Use only in patients receiving at least 60mg/24hours oral morphine equivalent for at least a week.
- The lozenge must be rotated in buccal pouch, not sucked. Older children will often choose to remove the lozenge before it is completely dissolved, giving them some much-valued control over their analgesia.

Fentanyl transdermal patches

- MHRA advises that *fentanyl* matrix patches must not be cut due to the risk of life threatening and potentially fatal opioid toxicity.
- Patches are not appropriate for initiation or titration phases of opioid management in palliative care due to large dose increments and time to achieve steady state.
- Initial evaluation of the analgesic effect cannot be made before the patch is worn for 24 hours.
- Patches should be changed every 72 hours and the site of application rotated. Some children who are rapid metabolisers need patch changes every 36-48 hours.
- After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore, after a dose increase, patients should wear the higher dose patch through two 72-hour applications before any further increase in dose level is made.
- After the patch is removed it may take 20 hours or more for serum fentanyl concentrations to decrease by 50% and significant blood concentrations persist for at least 24 hours. Replacement opioid therapy should therefore be initiated at a low dose and increased gradually
- Remove patches before MRI scanning: risk of burns.
- Absorption may be increased in pyrexia, vigorous exercise or topical application of heat including warm baths or showers
- For rapidly escalating symptoms in the last few hours and days of life, continue transdermal fentanyl and an additional 1/10 to 1/6 total daily oral morphine equivalent as required. If more than 2 PRN-doses are required in 24 hours, continue transdermal fentanyl and add morphine CSCI at a dose equivalent to the total daily morphine dose administered over the previous 24

hours. Adjust the PRN-dose taking into account the total opioid dose (i.e. transdermal fentanyl + continuous subcutaneous morphine).

Available as

- Intranasal spray Instanyl® (50micrograms/spray, 100micrograms/spray and 200micrograms/ spray). PecFent® (100micrograms/ spray and 400micrograms/spray).
- Lozenge with oromucosal applicator Actiq®, Cynril® (200micrograms, 400micrograms, 600micrograms, 800micrograms, 1.2mg and 1.6mg).
- Buccal/sublingual tablets Abstral®(100 micrograms, 200 micrograms, 300 micrograms, 400 micrograms, 600 micrograms and 800micrograms) and buccal tablets Effentora(R) (100 micrograms, 200 micrograms, 400 micrograms, 600 micrograms and 800micrograms).
- Patches: various manufacturers (12micrograms/hour, 25micrograms/hour, 37.5micrograms/hour, 50micrograms/hour, 75micrograms/hour, 100micrograms/hour); Ionys® transdermal system (40micrograms/dose)
- Injection: 50micrograms per ml

CD

- Schedule 2 CD

Evidence: (1–3,62,63,147–154)

Fluconazole

Use:

- Mucosal candidiasis infection (if nystatin not tolerated / effective), invasive candidal infections or prevention of fungal infections in immunocompromised patients

Dose and route:

Mucosal candidal infection

By mouth or intravenous infusion:

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

Continue treatment for 7-14 days in oropharyngeal candidiasis and 14-30 days in other mucosal infections.

Invasive candidal infections and cryptococcal infections

By mouth or intravenous infusion:

- **Neonate up to 13 days**: 6-12mg/kg every 72 hours
- **Neonate 14-28 days**: 6-12mg/kg every 48 hours
- **Child 1 month and over**: 6-12mg/kg every 24 hours maximum 800mg daily

Continue treatment for a minimum of 8 weeks with duration of treatment determined by response.

Prevention of fungal infections in immunocompromised patients

By mouth or intravenous infusion

- **Neonate up to 13 days**: 3-12mg/kg every 72 hours
- **Neonate 14-28 days**: 3-12mg/kg every 48 hours
- **Child 1 month and over**: 3-12mg/kg every 24 hours, maximum 400mg daily

Commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range.

Notes:

- Fungistatic anti-fungal.

Licensing

- Licensed for treatment of fungal infections in all ages

Therapeutics

- Resistance may develop with long-term treatment. Use for 7-14 days in oropharyngeal candidiasis. Use for 14-30 days in other mucosal infections.

Side effects

- Most frequent (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

Interactions

- Potent inhibitor of cytochrome P450 enzyme CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Increases levels of drugs metabolised by these enzymes including alfentanil, buprenorphine, carbamazepine, dexamethasone, diazepam, diclofenac, fentanyl, midazolam and omeprazole. *This list is not exhaustive-seek advice.*

Administration

- Intravenous infusion should be administered over 10–30 minutes at a rate not exceeding 5–10ml/minute
- Oral suspension may be administered via NG tube gastrostomy or jejunostomy. Bioavailability is unaffected by jejunal administration. Flush tube well after suspension is administered.

Patient information

- See Medicines for Children leaflet “Fluconazole for yeast and fungal infections” https://www.medicinesforchildren.org.uk/medicines/fluconazole-for-yeast-and-fungal-infections/

Available as

- Capsules (50mg, 150mg, 200mg); oral suspension (50mg/5ml, 200mg/5ml) and IV infusion (2mg/ml in 25ml, 50ml, 100ml).

Evidence: (1,2,8,155)

Fluoxetine

Use:

- Major depression (seek specialist advice)

Dose and route:

By mouth:

- **Child 5 years and over**: Initial dose 10mg once daily. May be increased after 1-2 weeks if necessary to a maximum of 20mg once daily.

Notes:

- Selective serotonin reuptake inhibitor (SSRI).

Licensing

- Licensed for use in children from 8 years of age.

Therapeutics

- Onset of benefit 3-4 weeks in depression
- Consider long half-life when adjusting dosage.
- Do not discontinue abruptly.
- May be beneficial in neuropathic pain and intractable cough.
- Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

Contraindications, cautions

- Caution in children: seek specialist advice. Caution in cardiac disease and poorly controlled epilepsy.

Side effects

- Increased risk of bleeding due to antiplatelet function.
- Increased risk of anxiety for first 2 weeks.
- Suicide related behaviours have been more frequently observed in clinical trials among children and adolescents treated with antidepressants compared with placebo. Mania and hypomania have been commonly reported in paediatric trials.
- Headache, nausea, insomnia, fatigue and diarrhoea.
- Movement disorders
- Increased risk of seizures

Interactions

- Inhibits cytochrome P450 enzymes CYP2C19 and CYP2D6. Increases levels of drugs metabolised by these enzymes including amitriptyline, carbamazepine, diazepam and erythromycin. *This list is not exhaustive –seek advice.*
- Must not be used in combination with a MAOI: risk of serotonin syndrome

Administration

- Oral liquid may be administered via NG tube or gastrostomy. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet “Fluoxetine for depression, obsessive compulsive disorder and bulimia nervosa” https://www.medicinesforchildren.org.uk/medicines/fluoxetine-for-obsessive-compulsive-disorder-ocd-depression-and-bulimia-nervosa/

Available as

- Capsules (10mg, 20mg, 30mg, 40mg, 60mg) dispersible tablets (20mg) and oral liquid (20mg/5ml).

Evidence: (1–3,156)

Gabapentin

Use:

- Adjuvant in neuropathic pain
- CNS irritability
- Visceral hyperalgesia
- Management of abnormal tone and movement disorders
- Uraemic Itch
- Intractable hiccup
- Epilepsy
- Restless legs syndrome in chronic kidney disease

Important safety information

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

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

Dose and route:

Neuropathic pain, all indications other than epilepsy

By mouth:

Consider introducing gabapentin more slowly in debilitated patients, or when administered with other CNS depressants

- **Neonate-23 months**: 5mg/kg/dose. Administer once daily on day 1, administer twice daily on day 2 then three times daily from day 3 onwards.

  Increase further, if necessary, in increments of 5-10mg/kg in 3 divided doses, every 3–7 days. Maximum 10mg/kg/dose

- **Child 2-11 years**: 5-10mg/kg/dose, maximum single dose 300mg. Administer once daily on day 1, administer twice daily on day 2 then three times daily from day 3 onwards.

  Increase further, if necessary, in increments of 5–10mg/kg in 3 divided doses, every 3–7 days. Maximum 20mg/kg/dose. Maximum single dose 600mg

- **12 years and over**: Initially 300mg once daily on day 1, then 300mg twice daily on day 2, then 300mg three times daily from day 3 onwards.

  Increase further, if necessary in steps of 300mg every 3-7 days given in 3 divided doses daily. Maximum 3600mg total daily dose

Gabapentin to pregabalin switch for neuropathic pain

See Appendix 5

Epilepsy

Consult BNFc or local neurology protocols. Gabapentin is now rarely used as a primary treatment for epilepsy.

Notes:

Licensing

- Licensed as an adjunct for the treatment of focal seizures in patients over 6 years and as a monotherapy for the treatment of focal seizures in patients over 12 years. Maximum licensed dose 50mg/kg/day for under 12 years. Not licensed for neuropathic pain in children.

Therapeutics

- Animal evidence suggests anti-seizure and analgesic activity of gabapentin is mediated via binding to the alpha-2 subunit of voltage gated calcium channels in the CNS with subsequent inhibition of excitatory neurotransmitter release and/or inhibition of descending inhibitory pain pathways.
- Doses can be titrated more slowly with increases every 1–2 weeks in in debilitated patients or co-administration with other CNS depressants
- Higher doses (up to 20mg/kg TDS) have been used in the management of severe dystonia. These higher doses are reached by slow upwards titration guided by the child's response.
- No consensus on dose for neuropathic pain. Doses shown are based on doses for partial seizures and authors' experience.
- Adult evidence for use in pruritus in anaemia, anxiety, hot flushes, sweating, refractory hiccups, restless legs syndrome and refractory cough.
- Risk of dependence and diversion for substance abuse

Side effects

- Very common (>1 in 10) side effects: somnolence, dizziness, ataxia, viral infection, fatigue, fever.

Pharmacokinetics

- Oral bioavailability of approximately 60%. However gabapentin absorption is saturable, leading to a non-linear pharmacokinetic profile and decrease in bioavailability with increasing gabapentin dose. Bioavailability also varies with patient population. Careful titration of dose is required.
- Peak plasma concentrations occur 2-3 hours after oral dosing.
- Bioavailability is not affected by food. Co-administration with antacids containing aluminium and magnesium can reduce bioavailability by up to 24%. Manufacturers recommend giving gabapentin two hours after antacids.

Hepatic impairment, renal impairment

- Gabapentin is solely excreted unchanged by the kidneys. Reduce dose in renal impairment (consult manufacturer's literature).

Interactions

- Morphine may increase gabapentin concentrations. Consider reducing the dose of gabapentin or opioids as clinically appropriate.

Administration

- Capsules can be opened and suspended in water or fruit juice (to hide the bitter taste) as an alternative to oral solution.
- Absorbed in proximal small bowel. The oral solution or the capsule contents (dispersed in water) can be given via a NG tube or gastrostomy. Flush tube well after administration.
- No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet "Gabapentin for neuropathic pain": https://www.medicinesforchildren.org.uk/gabapentin-for-neuropathic-pain and "Gabapentin for preventing seizures" https://www.medicinesforchildren.org.uk/gabapentin-for-preventing-seizures

Available as

- Capsules (100mg, 300mg, 400mg); tablets (600mg, 800mg), oral solution 250mg/5 ml (Neurontin, United States import). Oral solution 50mg/ml now available as licensed preparation in UK. May contain high amount of propylene glycol as an excipient

CD

- Schedule 3 CD but exempt from safe custody requirements.

Evidence: (1,2,8,157–162)

Gaviscon®

Use:

- Gastro-oesophageal reflux, dyspepsia and heartburn.

Dose and route:

By mouth:

Gaviscon Infant® (sodium alginate with magnesium alginate) sachets:

- **Neonate-2 years, body-weight less than 4.5kg**: 1 dose (half dual sachet) when required mixed with feeds or with water for breast fed babies, maximum 6 doses in 24 hours
- **Neonate-2 years, body-weight 4.5kg and over**: 2 doses (1 dual sachet) when required mixed with feeds or with water for breast fed babies or older infants, maximum 12 doses (6 dual sachets) in 24 hours

Gaviscon Liquid and Tablets (Sodium alginate, calcium carbonate, sodium bicarbonate)

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

Gaviscon Advance (Sodium alginate, potassium bicarbonate)

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

Notes:

Licensing

- Gaviscon Infant Sachets licensed for infants and young children up to 2 years of age, but use under 1 year only under medical supervision. Gaviscon liquid and tablets are licensed for use from 2 years of age but age 2-6 years only on medical advice. Gaviscon Advance suspension and tablets are licensed for use from 12 years of age; use under 12 years on medical advice only.

Contraindications, cautions

- Gaviscon Infant should not to be used with feed thickeners, nor in patients with excessive fluid losses (e.g. fever, diarrhoea, vomiting).
- Gaviscon Liquid contains 3.1mmol sodium per 5ml; Gaviscon tablets contain 2.65mmol sodium and also contain aspartame. Gaviscon Infant Sachets contain 0.92mmol sodium per dose (half dual sachet).

Administration

- Can be administered via nasogastric tube or gastrostomy. Calcium may bind to any phosphate in an enteral feed causing tube blockage. A prolonged break in feeding is not required, but the tube should be adequately flushed to ensure that the calcium supplement does not come into contact with the feed. Not appropriate for administration via jejunostomy.

Patient information

- See Medicines for Children leaflet “Gaviscon for gastro-oesophageal reflux disease”: https://www.medicinesforchildren.org.uk/medicines/gaviscon-for-gastro-oesophageal-reflux-disease/

Available as

- Gaviscon liquid and tablets; Gaviscon Advance suspension and tablets; Infant Sachets (comes as dual sachets, each half of dual sachet is considered one dose).

Evidence: (1,2,11,130)

Glycerol (glycerin)

Use:

- Constipation

Dose and routes

By rectum:

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

Notes:

- Hygroscopic and lubricant actions. May also be a rectal stimulant.

Licensing

- 1g suppositories licensed for use in infants up to 1 year of age, 2g suppositories licensed for use in children aged 1-11 years, 4g suppositories licensed for use from 12 years of age.

Side effects

- Associated with necrotising enterocolitis in babies less than 34 weeks gestation.

Pharmacokinetics

- Response usually in 20 minutes to 3 hours.

Administration

- Moisten with water before insertion.

Patient information

- See Medicines for Children leaflet “Glycerin (glycerol) suppositories for constipation” https://www.medicinesforchildren.org.uk/medicines/glycerin-glycerol-suppositories-for-constipation/

Available as

- Suppositories (1g, 2g, and 4g)

Evidence: (1,2,11)

Glycopyrronium bromide

Use:

- Control of upper airways secretions
- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation and drooling
- Bowel colic pain
- Paraneoplastic sweating or pyrexia

Dose and route:

By mouth:

Using ***Sialanar*®** glycopyrronium *bromide* 400micrograms/ml oral solution

- **Child 1 month and over**: 16micrograms/kg 3 times daily, increased in steps of 16micrograms/kg 3 times daily, every 7 days, adjusted according to response

  Maximum 80micrograms/kg 3 times daily, maximum 2.4mg/dose

Using **generic** 1mg/5ml oral solution

- **Child 1 month and over**: 20micrograms/kg 3 times daily, increased in steps of 20micrograms/kg 3 times daily, every 5-7 days, adjusted according to response

  Maximum 100micrograms/kg 3 times daily, maximum 3mg/dose

By subcutaneous or intravenous injection:

- **Child 1 month-11 years**: Initial dose of 4micrograms/kg 3-4 times daily. The dose may be increased as necessary to 10micrograms/kg 3-4 times daily,

  Maximum 200micrograms/dose 4 times daily

- **12 years and over**: 200micrograms 3-4 times daily

By continuous subcutaneous or intravenous infusion:

- **Child 1 month-11 years**: Initial dose of 12micrograms/kg/24hours, increased as necessary to 40micrograms/kg/24hours, maximum 1.2mg/24hours

- **12 years and over**: 600micrograms/24hours, increased as necessary to 1.2mg/24hours.

Notes:

- Antimuscarinic

Licensing

- Licensed oral solutions (Sialanar®, generic) are licensed for use in children from 3 years of age with a chronic neurological disorder, for chronic pathological drooling. Not licensed for use in children for control of upper airways secretion and hypersalivation.

Therapeutics

- Excessive secretions can distress the child, but more often distress those around him/her.
- Treatment is more effective if started before secretions become too much of a problem.
- More frequent subcutaneous administration, up to hourly, is occasionally required in adults.
- Adult evidence for use in smooth muscle spasm (e.g. intestine, bladder), inoperable intestinal obstruction, hyperhidrosis, para-neoplastic pyrexia and sweating.
- Injection solution has also been given sublingually in adults using same doses as subcutaneous or intravenous bolus

Side effects

- Antimuscarinic side effects including constipation, urinary retention, tachycardia, blurred vision

Pharmacokinetics

- Does not cross the blood brain barrier and therefore has fewer side effects than hyoscine hydrobromide, which is also used for this purpose. Also fewer cardiac side effects.
- Slower onset response than with hyoscine hydrobromide or butylbromide.
- Oral absorption of glycopyrronium is very poor with wide inter-individual variation.

Renal impairment

- Risk of accumulation: reduce dose or avoid

Administration

- Administration by CSCI: good compatibility data available for mixing with other commonly used palliative agents.
- Co-administration with food results in a marked decrease in systemic medicinal product exposure. Dosing should be at least one hour before or at least two hours after meals, or at consistent times with respect to food intake. High fat food should be avoided. Where the child's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake.
- Tablets may be dispersed in water immediately prior to administration via feeding tubes, or use the oral solution. Flush tube immediately with 10-20 ml water. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (1mg, 2mg), oral solution 200micrograms/ml as glycopyrronium bromide (various) and 400micrograms/ml as glycopyrronium *bromide* (Sialanar®), injection (200micrograms/ml 1ml and 3ml ampoules).
- Glycopyrronium bromide tablets and oral solutions are not interchangeable on a microgram-for-microgram basis due to differences in bioavailability. Sialanar® oral solution has approximately 25% higher bioavailability and therefore equivalent doses will be lower than for tablets and generic oral solutions. The prescriber should state the specific branded or generic oral preparation to be used; care should be taken if switching between oral preparations and dosing adjusted accordingly.

Evidence: (1–3,39,42,113,163)

Haloperidol

Use:

- Nausea and vomiting where cause is metabolic, or in difficult to manage cases such as end stage renal failure.
- Delirium
- Agitation in the last hours and days of life.
- Intractable hiccups.
- Psychosis (including steroid-induced), hallucinations.
- Persistent severe aggression in autism or pervasive developmental disorders (under specialist supervision).

Dose and route:

Nausea and vomiting, delirium, agitation at end of life:

By mouth

- **Child 1 month-11 years**: 20micrograms/kg/dose, maximum 1mg, once daily at night, increased as necessary to a maximum of 180micrograms/kg/dose, maximum 10mg. Can also be given in 2 or 3 divided doses
- **12 years and over**: 1mg once daily at night, increased as necessary to 10mg at night. Can also be given in 2 or 3 divided doses

By continuous intravenous or subcutaneous infusion

- **Child 1 month-11 years**: 20micrograms/kg/24hours (maximum 1mg/24hours), increased as necessary to a maximum of 90micrograms/kg/24hours
- **12 years and over**: Initial dose of 1mg/24hours. The dose may be increased as necessary to a maximum of 5mg/24hours.

Intractable hiccups

By mouth

- **Child 1 month-11 years**: 20micrograms/kg/dose (maximum 1mg) 3 times daily, increased as necessary to a maximum of 60micrograms/kg/dose (maximum 3mg) 3 times daily. Once hiccups are controlled reduce to stop or to lowest possible maintenance dose.
- **12 years and over**: 1mg 3 times daily, increased as necessary to maximum 3mg 3 times daily. Reduce to stop or to lowest possible maintenance dose once hiccups are controlled.

Notes:

- D2 receptor antagonist and typical antipsychotic.

Licensing

- Not licensed for use in children with nausea and vomiting, restlessness and confusion or intractable hiccups. Injection is licensed only for intramuscular administration in adults

Therapeutics

- Higher doses may be used under specialist advice. If nausea and vomiting are not controlled on maximal doses via continuous infusion, review cause(s) and consider changing to levomepromazine
- For dosage in psychosis discuss with child psychiatrist.
- Dosages for agitation and confusion are often higher.
- Adult dosages can exceed 15mg/24hours in severe agitation
- Oral solution (2mg/ml) has also been given sublingually using same doses as oral or rectal routes

Contraindications, cautions

- Contraindicated in congenital long QT syndrome; history of Torsade de Pointes; history of ventricular arrhythmia; QTc-interval prolongation
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, electrolyte imbalance or taking other drugs known to prolong the QT-interval

Side effects

- Associated with prolonged QT-interval and Torsades de Pointes, particularly if given intravenously or at higher than recommended doses.
- Side effects vary between age groups, with behavioural problems being common in children.
- Extrapyramidal side effects, neuroleptic malignant syndrome

Pharmacokinetics

- Oral bioavailability approximately 50%. Consider reducing dose when converting from oral to intravenous or subcutaneous routes

Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by drugs that inhibit this enzyme including erythromycin and fluconazole. Levels may be reduced by drugs that induce this enzyme.

Administration

- Oral solutions may be administered via feeding tubes without further dilution. Flush tube well following administration. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (500 micrograms, 1.5mg, 5mg, 10mg), capsules (500 micrograms), oral liquid (200 micrograms/ml, 1mg/ml, 2mg/ml), and injection (5mg/ml).

Evidence: (1–3,8,87,113,164)

Hydromorphone

Use:

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

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in patients already receiving regular strong opioids

By mouth using immediate release preparations

Convert using oral morphine equivalent (OME) from previous opioid analgesia, see Appendix 1

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Hydromorphone oral	5:1	Divide 24hour morphine dose by 5	Morphine oral 10mg ÷ 5 = hydromorphone oral 2mg

By mouth using modified release preparations

- Calculate the total daily dose (regular + PRN) of oral hydromorphone administered over the previous 24 hours once the patient is established on regular hydromorphone for 2-3 days

  12-hourly preparations: Divide the total daily dose of oral hydromorphone by two and administer every 12 hours

  Consider reducing the dose of hydromorphine by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

  Ensure continued access to immediate release hydromorphone as required for breakthrough pain, see below.

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of opioid administered over the previous 24 hours

  Convert to the equivalent dose of CSCI hydromorphone using the table

Conversion		**Ratio**	**Calculation**	**Example**
From	**To**			
Morphine oral	Hydromorphone CSCI or CIVI	10:1	Divide 24hour morphine dose by 10	Morphine oral 30mg ÷ 10 = hydromorphone CSCI 3mg
Morphine CSCI or CIVI	Hydromorphone CSCI or CIVI	5:1	Divide 24hour morphine dose by 5	Morphine CSCI 25mg ÷ 5 = hydromorphone CSCI 5mg
Hydromorphone Oral	Hydromorphone CSCI or CIVI	2:1	Divide 24hour hydromorphone dose by 2	Hydromorphone 10mg oral ÷ 2 = CSCI 5mg hydromorphone

  Consider reducing the dose of hydromorphone by 25-50% when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

  Ensure continued access to immediate release hydromorphone as required for breakthrough pain see below

Breakthrough Pain in patients already receiving regular strong opioids

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10 to 1/6 of total daily hydromorphone dose every 1-4 hours as required.
- If the route for breakthrough analgesia is different to the route for background analgesia (e.g. CSCI with oral breakthrough) convert the breakthrough dose as above to the required route

Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

Pain in opioid naïve patients

By mouth:

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child 1 year and above**: 25micrograms/kg per dose maximum 2mg per dose every 4 hours increasing as required.
- **12 years and above:** 1.3mg every 4 hours increasing as required

By subcutaneous or slow intravenous injection:

- **Child 1 year and above**: 12micrograms/kg per dose every 4 hours, increasing as required

Notes:

- Analogue of morphine with similar pharmacokinetic and pharmacodynamics

Licensing

- Licensed for the relief of severe pain in cancer in adults and adolescents aged over 12 years.

Side effects

- Usual opioid side effects

Pharmacokinetics

- Oral bioavailability 37-62% (wide inter-individual variation).
- Onset of action 15 min for SC, 30 min for oral. Peak plasma concentration 1 hour orally.
- Main metabolite is hydromorphone-3-glucuronide (H3G). H3G has no analgesic activity but, like morphine-3-glucuronide (see morphine), it is a CNS neuro-excitant.
- All metabolites are renally excreted and can accumulate in renal impairment.
- More soluble than morphine, and available as a high-concentration injection (50mg/ml). Alternative to diamorphine when high doses need to be administered by CSCI
- Plasma half- life 2.5 hours early phase, prolonged late phase: duration of action 4-5 hours.
- Equianalgesic ratios vary more than for other opioids: possibly due to inter-individual variation in metabolism or bioavailability.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Hepatic impairment, renal impairment

- Caution in hepatic impairment, use at reduced doses. Avoid in severe hepatic impairment
- Caution in renal impairment, use at reduced starting doses.

Administration

- For CSCI dilute with water for injection, sodium chloride 0.9% or glucose 5%.
- Modified release capsules are given 12-hourly.

- Capsules (both types) can be opened and contents sprinkled on soft food. Do not administer via feeding tubes due to risk of blockage

Available as

- Capsules (1.3mg, 2.6mg) and modified release capsules (2mg, 4mg, 8mg, 16mg, 24mg). Injection (2mg/ml, 10mg/ml, 20mg/ml and 50mg/ml). Oral solution available as a manufacturer's special.

CD

- CD schedule 2

Evidence: (1–3,62,63,165–167)

Hyoscine butylbromide (Buscopan)

Use:

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

Dose and route:

Adjuvant in smooth muscle spasm of the gastrointestinal tract

By mouth

- **Child 1 month-1 year**: 300-500micrograms/kg 3–4 times daily, maximum 5mg per dose
- **Child 2 -4 years**: 5mg 3–4 times daily
- **5- 11 years**: 10mg 3–4 times daily
- **12 years and over**: 10–20mg 3–4 times daily

By subcutaneous bolus injection, intravenous injection or intramuscular injection

- **Child 1 month- 4 years**: 300–500micrograms/kg 3-4 times daily, maximum 5mg per dose
- **5-11 years**: 5–10mg 3–4 times daily
- **12 years and over:** 10–20mg 3–4 times daily

By continuous subcutaneous infusion:

- **Child 1 month- 4 years:** 1.5mg/kg/24hours (max 15mg/24hours)
- **Child 5-11 years**: 30mg/24hours
- **12 years and over**: Up to 60-80mg/24hours

Higher doses may be needed; doses used in adults range from 20-120mg/24hours. Maximum dose 300mg/24hours.

Adjuvant in smooth muscle spasm of gastrointestinal and urinary tract, antisecretory effect in bowel obstruction, management of respiratory secretions

By subcutaneous bolus injection, intravenous injection or intramuscular injection

- **Child 1 month-4 years**: 300–500micrograms/kg 3-4 times daily, maximum 5mg per dose
- **Child 5-11 years**: 5–10mg 3–4 times daily
- **12 years and over:** 10– 20mg 3–4 times daily

By continuous subcutaneous infusion:

- **Child 1 month- 4 years:** 1.5mg/kg/24hours (max 15mg/24hours)
- **Child 5-11 years**: 30mg/24hours
- **12 years and over**: Up to 60-80mg/24hours

Higher doses may be needed; doses used in adults range from 20-120mg/24hours. Maximum dose 300mg/24hours.

Notes:

- Antimuscarinic and has smooth muscle relaxant and antisecretory properties

Licensing

- Tablets are not licensed for use in children <6 years old. Injection is not licensed for use in children.

Therapeutics

- Does not cross blood brain barrier (unlike hyoscine hydrobromide), hence no central antiemetic effect and doesn't cause drowsiness.
- More likely to be effective in death rattle if used prophylactically

Contraindications, cautions

- Contraindicated in patients with tachycardia. Caution in cardiac disease. The MHRA recommends that patients with cardiac disease are monitored and that resuscitation equipment and trained personnel are readily available: this may not be appropriate in end of life care
- Increased risk of cardiac arrhythmia and anaphylaxis in patients with underlying cardiac disease.
- Likely to exacerbate gastro-oesophageal reflux

Side effects

- Anti-muscarinic side effects including constipation, urinary retention, tachycardia, blurred vision.

Pharmacokinetics

- Onset of action less than 10 min for SC/IV; 1-2 hours orally. Time to peak plasma concentration 15 min-2 hours orally. Plasma half-life 1-5 hours. Duration of action less than 2 hours in adult volunteers but possibly longer in moribund patients.
- Oral bioavailability, based on urinary excretion, is <1%. Thus, any antispasmodic effect reported after oral administration probably relates to a local contact effect on the GI mucosa.

Administration

- Injection solution may be given orally or via an enteral feeding tube. Administration via jejunostomy bypasses local effects on GI tract and is not recommended. Injection solution can be stored for 24 hours in the refrigerator after opening.
- Slow IV injection over 1 minute, diluted with glucose 5% or sodium chloride 0.9%.

Available as

- Tablets (10mg) and injection (20mg/ml).

Evidence: (1–3,8,42,163,168,169)

Hyoscine hydrobromide

Use:

- Control of upper airways secretions
- Noisy breathing at the end of life (may be more effective if started early)
- Hypersalivation and drooling
- Bowel colic pain
- Paraneoplastic sweating or pyrexia

Dose and routes

By mouth or buccal route:

- **Child 1 month- 11 years**: 10micrograms/kg, maximum 600micrograms, 4 times daily
- **12 years and over**: 300micrograms 4 times daily, increased gradually to a maximum of 600micrograms 4 times daily if required

By transdermal route:

- **Neonate over 32 weeks corrected gestational age, child up to 2 years**: 250micrograms (1/4 x 1mg/72hour patch) every 72 hours
- **Child 3-9 years**: 500micrograms (1/2 x 1mg/72hours patch) every 72 hours
- **10 years and over**: 1mg (1 x 1mg/72hours patch) every 72 hours

By subcutaneous or intravenous injection or infusion:

- **Child 1 month-17 years**:

  10micrograms/kg, maximum 600micrograms, every 4–8 hours

  OR 40-60micrograms/kg/24hours via CSCI/IV infusion.

  Maximum suggested dose is 2.4mg in 24 hours: higher doses may be used by specialist units.

Notes:

- Antimuscarinic with smooth muscle relaxant and antisecretory properties

Licensing

- Not licensed for use in children for control of upper airways secretion or hypersalivation.

Therapeutics

- Higher doses often used under specialist advice.
- Second line, after glycopyrronium bromide, for treatment of hypersalivation in cerebral palsy

Contraindications, cautions

- MHRA (July 2023): Hyoscine hydrobromide patches (Scopoderm 1.5mg Patch or Scopoderm TTS Patch): risk of anticholinergic side effects, including hyperthermia particularly when used outside the product licence
- Transdermal patches contain metal in the backing and must be removed before MRI scanning to avoid burns.

Side effects

- Side effects: common or very common: confusion; constipation; dizziness; drowsiness; dry mouth; dyspepsia; flushing; headache; nausea; palpitations; skin reactions; tachycardia; urinary disorders; vision disorders; vomiting. Frequency unknown: neuroleptic malignant syndrome

Administration

- Apply patch to hairless area of skin behind ear.
- The patch can cause alteration of the pupil size on the side it is placed.
- Manufacturers of Scopoderm TTS patch have confirmed that it is safe to cut patches although this is outside the scope of product licence
- Injection solution may be administered orally and via feeding tubes. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (150micrograms, 300micrograms), patches (releasing 1mg/72 hours), and injection (400micrograms/ml, 600micrograms/ml).
- An oral solution is available via a ‘specials’ manufacturer.

Evidence: (1,2,42,170,171)

Ibuprofen

Use:

- Non-steroidal analgesic
- Anti-pyretic
- Adjuvant for musculoskeletal pain.

Dose and routes

Pain and inflammation

By mouth using immediate release preparations

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

By mouth using modified release preparations

- **12 years and over**: 1.6g once daily, dose preferably taken in the early evening, increased to 2.4g daily in 2 divided doses if necessary.

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

By mouth using immediate release preparations

- **Child aged 3 months and over**: 30–40mg/kg daily in 3–6 divided doses preferably after food. Increased, if necessary to a maximum of 60mg/kg/day. Maximum daily dose 2.4g

Notes:

- Non-opioid analgesic, NSAID and non-selective COX inhibitor

Licensing:

- Orphan drug licence for closure of ductus arteriosus in preterm neonate. Not licensed for use in children less than 3 months of age or body-weight less than 5kg, except for up to two doses for post immunisation pyrexia. (50mg/dose given a minimum of 6 hours apart). Topical preparations and granules are not licensed for use in children.

Therapeutics

- Combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side effects than other NSAIDs but its anti-inflammatory properties are weaker.
- Alternating or combining with paracetamol may give better antipyretic effect than monotherapy but benefits in terms of analgesia are unclear.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

Contraindications, cautions

- Caution in patients with or at risk of thrombocytopenia: may impair platelet function.
- May mask fever and other signs of inflammation
- Will cause closure of ductus arteriosus; contraindicated in duct-dependent congenital heart disease
- Caution in cardiac, hepatic or renal impairment and those with asthma. Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

Side effects

- May be associated with an increased risk of thrombotic events (e.g. myocardial infarction, thrombotic stroke) in children.
- All NSAIDs are associated with gastro-intestinal toxicity however lowest risk is likely to be with ibuprofen. Consider prescription of a proton pump inhibitor with prolonged use.

Hepatic impairment, renal impairment:

- Avoid or use with caution in severe renal failure.

Administration

- For administration via an enteral feeding tube, use a liquid preparation; dilute with an equal volume of water immediately prior to administration where possible. No specific information for jejunal administration. Administer as above and monitor for any signs of loss of efficacy or increased side effects.
- Can be used topically particularly for sprains, strains and arthritis.

Patient information

- Patient information: See Medicines for Children leaflet: “Ibuprofen for pain and inflammation” https://www.medicinesforchildren.org.uk/medicines/ibuprofen-for-pain-and-inflammation /

Available as

- Tablets (200mg, 400mg, 600mg), modified release tablet (800mg), orodispersible tablets (200mg), chewable capsules (100mg), capsules (200mg, 400mg), modified release capsules (200mg, 300mg), oral syrup (100mg/5ml), granules (600mg/sachet), topical foam (50mg per 1g) creams and gels (5%).

Evidence: (1,2,8,11,172–174)

Ipratropium Bromide

Use:

- Wheeze or breathlessness caused by bronchospasm
- Rhinorrhoea associated with allergic and non-allergic rhinitis
- Localised management of sialorrhoea (with fewer systemic side effects)

Dose and routes:

Wheeze or breathlessness caused by bronchospasm

By inhalation of nebulised solution

- **Child 1 month-5 years**: 125-250micrograms as required maximum 1mg daily
- **Child 6-11 years**: 250micrograms as required maximum 1mg daily
- **12 years and over**: 500micrograms as required maximum 2mg daily

By aerosol inhalation

Use via large volume spacer (and a close-fitting face mask in children under 3 years).

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

Rhinorrhoea associated with allergic and non-allergic rhinitis

By intranasal administration

- **12 years and over**: 2 sprays 2–3 times daily, dose to be sprayed into each nostril.

Notes

Licensing

- Not licensed for severe or life-threatening acute asthma. Inhalvent® not licensed for use in children under 6 years. Not licensed for rhinorrhoea

Therapeutics

- In severe acute asthma, dose can be repeated every 20-30 minutes in first two hours, then every 4-6 hours as necessary (unlicensed).
- No evidence of efficacy in infection-related bronchospasm in infants
- Use in management of sialorrhea in children not well established

Side effects

- Anti-muscarinic side effects occur with systemic absorption, including constipation, urinary retention, tachycardia, blurred vision.

Pharmacokinetics

- Maximum effects 30-60 minutes after use. Duration of action 3-6 hours. Bronchodilation can usually be maintained with treatment 3 times daily.

Administration

- Inhaled product should be used with a suitable spacer device, and the child/carer should be given appropriate training. In acute asthma, use via an oxygen-driven nebuliser.

Available as

- Nebuliser solution (250micrograms in 1 ml, 500micrograms in 2 ml), aerosol inhaler (20micrograms per metered dose), nasal spray 21micrograms per metered dose.

Evidence: (1,2,175,176)

Ketamine

Use:

- Neuropathic pain and hyperalgesia
- Pain failing to respond to usual treatments, including opioids, non-opioids and adjuvant analgesics
- Adjuvant to strong opioids
- Severe visceral pain
- Ischaemic pain
- To reduce N-methyl-D-aspartate (NMDA) receptor wind-up pain and opioid tolerance.
- Emerging use in refractory status epilepticus.

Dose and routes

Pain including NMDA wind-up pain

By mouth, or buccal route

- **Neonate (over 37 weeks corrected gestational age)- child 11 years**: Starting dose 100micrograms/kg, as required or regularly 6–8 hourly. Increase in increments of 100micrograms/kg up to 400micrograms/kg as required.
- **12 years and over**: 5-10mg as required or regularly 6–8 hourly; increase in steps of 5-10mg up to 50mg/dose as required.

  Doses up to 200mg or 3mg/kg 4 times daily reported in adults

By continuous subcutaneous or intravenous infusion:

- **Child 1 month and over**: Starting dose 500micrograms/kg/24hours to 1mg/kg/24hours. Increase according to response; usual maximum 12mg/kg/24hours or 500mg/24hours

  Doses up to 60mg/kg/24hours have been reported, including in refractory status epilepticus.

By intravenous administration for anaesthesia

Seek specialist advice

Notes:

- Dissociative anaesthetic which has analgesic properties in sub-anaesthetic doses.
- Racemic mixture of the S(+) and R(–) stereoisomers of ketamine. The most potent NMDA-receptor–channel blocker available for clinical use

Licensing

- Not licensed for use in children with neuropathic pain.

Therapeutics

- Potential secondary benefits in adolescents with depressive symptoms.
- Continuous intravenous infusion of ketamine appears effective in refractory status epilepticus, but its place in clinical practice remains to be determined.
- Higher starting doses may be used, particularly by infusion, in anaesthesia and acute postoperative pain
- Generally administered orally or subcutaneously in palliative care. Can also be administered via intramuscular, intravenous, buccal, intranasal, spinal and rectal routes.
- Has also been administered topically for mucositis and painful wounds although RCT evidence is lacking.
- Buccal dose is effective but bitter taste. May result in increased drowsiness and slightly lower efficacy due to lack of first pass metabolism
- S-ketamine is licensed in many countries: use 50% of doses quoted above
- Short courses are preferred to long term use due to cumulative adverse effects including cognitive impairment and also renal tract damage.
- Once analgesia has been obtained, an attempt should be made to withdraw ketamine over 2–3 weeks. The benefit from a short course can last for weeks or even months, and the course can be repeated if necessary.
- Alternatively ketamine can be given as a short “burst” increasing doses stepwise rapidly over a period of 3-4 days until a therapeutic effect is achieved or side effects prevent further dose escalation and then decreasing in a similar stepwise fashion to stop after 7-10 days
- Some practitioners routinely reduce the background opioid dose by 25–50% when starting parenteral ketamine.
- Sudden discontinuation may precipitate hyperalgesia or allodynia: discontinue gradually over 2-3 weeks after prolonged use.

Side effects

- Neuropsychiatric side effects including agitation, hallucinations, anxiety and dysphoria, diplopia, nystagmus and sleep disturbance. Animal studies indicate that ketamine can induce neuronal cell death in the immature brain. Emergent phenomena occur to a lesser extent with the sub-anaesthetic analgesic doses given in palliative care, and generally can be controlled by concurrent administration of a benzodiazepine (e.g. diazepam, midazolam) or haloperidol.
- Gastrointestinal side effects include vomiting, abdominal pain, gastrointestinal bleeding, abnormal liver function tests and biliary duct dilatation
- Urological side effects include urinary frequency, urgency, dysuria, and haematuria

Pharmacokinetics

- Wide variation in clearance, mostly explained by genetic polymorphism in the activity of CYP2B6 together with increasing age
- Oral bioavailability is approximately 20% but ketamine is potentiated by first pass metabolism. In practical terms it is therefore reasonable to use a 1 to 1 ratio for conversion between oral and subcutaneous or intravenous routes.
- Onset of action 5 min IM; 15-30 min SC; 30 min PO. Duration of action 30 min–2h IM; 4-6h PO, sometimes longer. Bio-availability 93% IM; 45% nasal; 30% SL; 30% PR; 20% PO.

Hepatic and renal impairment

- Causes hepatic enzyme induction and enhances its own metabolism. Caution in severe hepatic impairment, consider dose reduction.

Interactions

- Diazepam can increase the half-life and prolong the effects of ketamine.

Administration

- Buccal doses should be prepared in a maximum volume of 2 ml. The bitter taste may make this route unpalatable. Special preparations for buccal use are available in UK.
- Dilute in 0.9% sodium chloride for subcutaneous or intravenous infusion. Can be administered as a separate infusion or by adding to opioid infusion/ PCA/NCA.
- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Injection (10mg/ml, 50mg/ml, 100mg/ml) and oral solution (50mg in 5ml) from a 'specials' manufacturer. Injection solution may be given orally. Mix with a flavoured soft drink to mask the bitter taste.

CD

- Schedule 2 CD.

Evidence: (1–3,165,177–184)

Ketorolac

Use:

- Short-term management of moderate to severe acute postoperative pain
- Chronic pain: limited experience of extended use

Doses and routes:

By intravenous or subcutaneous bolus

- **Child 1-15 years**: 500microgam/kg, maximum 15mg, repeated every 6 hours as required; maximum 60mg daily
- **16 years and over, body-weight over 50kg**: 10mg, every 4–6 hours as required: increased gradually to maximum of 90mg daily

By buccal route, using injection solution

- **Child 1 year and over**: 500micrograms/kg, maximum 15mg, up to 4 times daily

By continuous subcutaneous infusion

- **Child 1-15 years**: 2mg/kg/24hours, maximum 60mg daily
- **16 years and over, body-weight over 50kg**: 60mg/24hours, increased gradually to a maximum of 90mg daily

Notes:

- Non-opioid, NSAID and preferential COX-1 inhibitor with potent analgesic effects, but only moderate anti-inflammatory action. Potency approximately twice that of naproxen.

Licensing

- Licensed only for the short-term management (maximum of 2 days) of moderate to severe acute postoperative pain in adults and adolescents from 16 years of age. Not licensed for subcutaneous or buccal administration

Therapeutics

- Limited, poor quality data for indications other than post-operative pain. Anecdotal reports of effectiveness for patients with bone pain unresponsive to oral NSAIDs. Use the lowest possible dose for the shortest possible time
- High risk of gastrointestinal toxicity: co-prescription of a proton pump inhibitor strongly recommended.

Contraindications, cautions

- Contraindicated in hypersensitivity to ketorolac or other NSAIDs; history of asthma; active peptic ulcer or history of GI bleeding; severe heart, hepatic or renal failure; suspected or confirmed

cerebrovascular bleeding or coagulation disorders. Do not use in combination with any other NSAID.
- May mask fever and other signs of inflammation

Side effects

- May be associated with increased risk of thrombotic events (e.g. myocardial infarction, thrombotic stroke) in children.
- All NSAIDs are associated with gastro-intestinal toxicity. Ketorolac is in the highest risk group. Co-prescription of a proton pump inhibitor is strongly recommended
- Other potential side effects; Very common (>10% patients): headache, dyspepsia, nausea, abdominal pain; Common (1-10% patients): dizziness, tinnitus, oedema, hypertension, anaemia, stomatitis, abnormal renal function, pruritus, purpura, rash, bleeding and pain at injection site. Risk of adverse effects likely to increase with prolonged use.

Interactions

- Anticoagulants (contraindicated as the combination may cause an enhanced anticoagulant effect); corticosteroids (increased risk of GI ulceration of bleeding); diuretics (risk of reduced diuretic effect and increase the risk of nephrotoxicity of NSAIDs); other potential nephrotoxic drugs.

Pharmacokinetics

- Onset of action 10-30mins IV/IM; maximal analgesia achieved within 1-2 hours and median duration of effect 4-6 hours.

Renal impairment

- Reduce dose or avoid.

Administration

- For administration by intravenous bolus administer neat or diluted in a small volume of 0.9% sodium chloride or 5% dextrose and give over at least 15 seconds
- Subcutaneous injection can be irritant therefore dilute to the largest volume possible (0.9% sodium chloride suggested). Alkaline in solution so high risk of incompatibility if mixed with acidic drugs. Some data for compatibility in 0.9% sodium chloride with diamorphine or oxycodone. ***Incompatibilities*** include with cyclizine, glycopyrronium, haloperidol, levomepromazine, midazolam and morphine.

Available as

- Injection 30mg/ml (injection contains ethanol as an excipient) and injection 10mg/ml.

Evidence: (1–3,185–189)

Lactulose

Use:

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

Dose and route:

Constipation:

By mouth:

- **Neonate**: 2.5ml twice daily, adjusted according to response
- **Child 1 month-11 months**: 2.5ml twice daily, adjusted according to response
- **Child 1-4 years:** 2.5-10ml twice daily, adjusted according to response
- **Child 5 years and over**: 5-20ml twice daily, adjusted according to response

Hepatic encephalopathy:

By mouth

- **12 years and over**: 30-50ml three times daily, adjusted to produce 2-3 soft stools per day

Notes:

- Osmotic laxative

Licensing

- Licensed for constipation in all age groups. Not licensed for hepatic encephalopathy in children.

Therapeutics

- Prebiotic: increases beneficial colonic bacteria (unlike macrogol). Macrogols are often preferable in palliative care but lactulose can be useful if large volumes are not tolerated. Generally unhelpful in opioid-induced constipation when a stimulant laxative is needed. Sickly taste. Unlikely to affect diabetic or ketogenic diets at conventional doses.

Contraindications, cautions

- Contraindicated in galactosaemia, intestinal obstruction.
- Caution in lactose intolerance.

Side effects

- Nausea, flatus, colic especially at high doses.

Pharmacokinetics

- Onset of action 36-48 hours.

Administration

- May be taken with water and other drinks. Dilute with 2-3 times the volume of water for administration via feeding tube. Therapeutic effect is unaffected by administration directly into the stomach or jejunum

Patient information

- See Medicines for Children leaflet: “Lactulose for constipation” https://www.medicinesforchildren.org.uk/medicines/lactulose-for-constipation/

Available as

- Oral solution

Evidence: (1–3,190,191)

Lansoprazole

Use:

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

Dose and routes:

By mouth

- **Child body-weight less than 30 kg**: 500micrograms/kg-1mg/kg, maximum 15mg, once daily in the morning
- **Child body-weight more than 30 kg**: 15-30mg once daily in the morning

Notes:

Gastric proton pump inhibitor

Licensing

- Not licensed in the UK for infants, children or adolescents. Licensed in the US from 1 year of age. Exact doses limited by available formulations.

Therapeutics

- Inhibition of gastric acid production is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Infants and children appear to need a higher mg/kg dose to achieve therapeutic acid suppression

Cautions

- FasTabs contain aspartame and should be used with caution in known PKU patients.

Side effects

- Common adverse effects (>1 in 100 to <1 in 10): headache, dizziness; nausea, diarrhoea, stomach pain, constipation, vomiting, flatulence, dry mouth, pharyngitis, increase in liver enzyme levels, urticaria, itching, rash. Hypomagnesaemia may develop with prolonged use. PPIs are an independent risk factor for Clostridium Difficile infection. MHRA safety warning 2015: there is a very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs.

Pharmacokinetics

- Oral bioavailability is good at 80-90% compared to 60% for omeprazole. Food slows down the absorption and decreases the bioavailability.

Hepatic impairment

- Reduce by 50% in moderate to severe hepatic impairment

Interactions

- Lansoprazole may interfere with absorption of drugs where bioavailability is significantly affected by gastric pH (e.g. atazanavir, itraconazole); may cause increase in digoxin levels and increase in plasma concentration of drugs metabolised by CYP3A4 (e.g. theophylline and tacrolimus). Drugs which inhibit or induce CYP2C19 or CYP3A4 may affect the plasma concentration of lansoprazole. Sucralfate and antacids may decrease the bioavailability of lansoprazole.

Administration

- Anecdotal evidence for halving Lansoprazole FasTabs to give a 7.5mg dose. For optimal effect, the single daily dose is best taken in the morning. Lansoprazole should be taken at least 30 minutes before food.
- Capsules: Capsules should be swallowed whole with liquid. Capsules may be opened and the granules mixed with a small amount of water, apple/tomato juice or sprinkled onto a small amount of soft food (e.g. yoghurt, apple puree) to ease administration.
- FasTabs: Place on the tongue and gently suck. FasTabs can be swallowed whole with water or mixed with a small amount of water if preferred.
- Lanzoprazole FasTabs can be dispersed in 10 ml water and administered via an 8Fr NG tube without blockage. For smaller bore tubes, dissolve the contents of a lansoprazole capsule in 8.4% sodium bicarbonate before administration. If the tube becomes blocked, use sodium bicarbonate to dissolve any enteric coated granules lodged in the tube. Lansoprazole less likely than omeprazole MUPS to cause blockage of small bore tubes. Administration into the jejunum is unlikely to reduce bioavailability.

Patient information

- See Medicines for Children leaflet: Lansoprazole for gastro-oesophageal reflux disease (GORD) and ulcers https://www.medicinesforchildren.org.uk/medicines/lansoprazole-for-gastro-oesophageal-reflux-disease-gord-and-ulcers/

Available as

- Capsules 15mg and 30mg and orodispersible tables 15mg and 30mg.

Evidence: (1–3,8,130,131)

Levetiracetam

Use:

- Focal seizures with or without secondary generalisation
- Epilepsy; maintenance treatment
- Convulsive status epilepticus

Dose and route:

Epilepsy: maintenance treatment

- Monotherapy of focal seizures with or without secondary generalisation
- Adjunctive therapy of focal seizures with or without secondary generalisation
- Adjunctive therapy of myoclonic seizures and tonic clonic seizures

By mouth or intermittent intravenous or subcutaneous infusion.

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

By continuous subcutaneous or intravenous Infusion

- Administer total daily oral or intravenous dose of levetiracetam as a continuous infusion/24hours

Convulsive status epilepticus

- APLS resuscitation guideline (2021) first choice long-acting anticonvulsant after 2 doses of benzodiazepine
- Full loading dose to be given EVEN if the child is already receiving maintenance levetiracetam

By intravenous or interosseous injection over 5 minutes

- **Child 1 month and over**: 40mg/kg, maximum 3g

  Dilute 1:1 with 0.9% sodium chloride, minimum volume 10ml

Notes:

Licensing

- Not licensed for convulsive status epilepticus. Granules not licensed for use in children under 6 years, for initial treatment in children with body-weight less than 25kg, or for the administration of doses below 250mg.

Therapeutics

- Phenobarbital, not levetiracetam, remains drug of first choice long acting anticonvulsant after 2 doses of benzodiazepine for neonatal seizures
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

Side effects

- Movement disorders, sedation, confusion, exacerbation of seizures, neuroleptic malignant syndrome

Interactions

- Caution when administering with other drugs with CNS depressant effects: decreases the clearance of Methotrexate

Administration

- Intravenous administration over 15 minutes at a suggested concentration of 2.5-15mg/ml. May be administered at a concentration of 50mg/ml over 5-15 minutes in an acute situation.
- Administration of levetiracetam by subcutaneous bolus or intermittent (over 15-30 minutes) or continuous subcutaneous infusion is off-label but with increasing supporting (low-grade) evidence.
- Dose conversion for oral:intravenous:subcutaneous is 1:1:1
- Continuous subcutaneous infusion: Injection has a low pH and high osmolality which increases the potential for irritation around the injection site. Dilute in water for injections or 0.9% sodium chloride to the maximum volume compatible with the infusion device. May be administered neat i.e. at a concentration of 100mg/ml but increased risk of site reactions.
- Limited compatibility data. Administer via a separate syringe driver where possible. Reported to be visually compatible at usual concentrations with diamorphine, hyoscine butylbromide, levomepromazine, midazolam, morphine or oxycodone. Seek specialist advice.

Patient information

- See Medicines for Children leaflet “Levetiracetam for preventing seizures” https://www.medicinesforchildren.org.uk/medicines/levetiracetam-for-preventing-seizures/

Available as

- Tablets 250mg, 500mg, 750mg and 1g; oral solution 100mg/ml; solution for infusion 100mg/ml. Also available as granule sachets for oral administration 250mg, 500mg, 750mg, 1g, 1.5g

Evidence: (1,2,192–199)

Levomepromazine

Use:

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

Dose and routes

Nausea and vomiting

By mouth:

- **Child 1 month-11 years**: 50-100micrograms/kg once daily, usually at night, or in two divided doses.

  Increase as required and tolerated in increments of 50–100micrograms/kg/24hours to a maximum of 400micrograms/kg/24hours.

- **12 years and over**: 2.5–5mg once daily, usually at night, or in two divided doses.

  Increase as required and tolerated in increments of 2.5–5mg to maximum of 25mg/24hours

By continuous intravenous or subcutaneous infusion over 24hours:

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

Infusion doses can also be given as intermittent intravenous or subcutaneous boluses in one or two divided doses

Sedation and confusion, refractory pain

By continuous subcutaneous or intravenous infusion over 24hours:

- **Child 1 year-11 years**: 350micrograms/kg/24hours, maximum initial dose 12.5mg, increasing as necessary up to 3mg/kg/24hours
- **12 years and over**: 12.5mg/24hours increasing as necessary up to 200mg/24hours.

Infusion doses can also be given as intermittent intravenous or subcutaneous boluses in one or two divided doses

Notes:

- Phenothiazine antihistamine with powerful sedative and antiemetic properties

Licensing

- Licensed for use in children with terminal illness for the relief of pain and accompanying anxiety and distress

Therapeutics

- Injection solution has also been given sublingually in adults using the same doses as oral route
- A low dose is often effective as an antiemetic. Higher doses are very sedative and not necessarily more effective as an antiemetic. Consider adding an additional antiemetic with a different mode of action e.g. dexamethasone, ondansetron.

Cautions

- May lower seizure threshold. Caution in cardiac disease, liver and renal impairment.
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval

Side effects

- Hypotension, particularly with higher doses. Very sedating, especially at high doses.
- Paradoxical agitation, movement disorders including neuroleptic malignant syndrome.
- Constipation, vomiting

Pharmacokinetics

- Oral bioavailability 50%; consider halving dose if converting oral to subcutaneous or intravenous route in stable patient

Renal impairment

- Reduce dose and administer once daily in severe renal impairment, titrating according to response

Interactions

- Potent inhibitor of cytochrome P450 enzyme CYP2D6. May increase levels of drugs metabolised by this enzyme including amitriptyline.

Administration

- Tablets may be halved or quartered to obtain smaller doses. Tablets/segments may be dispersed in water for administration via a NG or gastrostomy tube. Flush tube well after administration. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Dilute in sodium chloride 0.9% or water for injection for subcutaneous infusion. Anecdotally associated with an increased risk of site reactions.

Available as

- Tablets (25mg) and injection (25mg/mL).

Evidence: (1–3,8,113,200–203)

Lidocaine (Lignocaine) plaster

Use:

- Localised neuropathic pain

Dose and routes

Topical:

- **Child 3-17 years**: Apply 1-2 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period
- **Adult 18 years and over**: Apply up to 3 plasters to affected area(s). Apply plaster once daily for 12 hours followed by 12 hours plaster free period

Notes:

Licensing

- Not licensed for use in children or adolescents under 18 years. Doses extrapolated from adult BNF

Therapeutics

- Lidocaine in the plaster diffuses continuously into the skin, providing a local analgesic effect. Putative mechanism of action: stabilisation of neuronal membranes by down-regulation of sodium channels
- Adult recommended maximum 3 plasters per application.
- When lidocaine 5% medicated plaster is used according to the maximum recommended dose (3 plasters applied simultaneously for 12 hours) about 3± 2% of the total applied lidocaine dose is systemically available and is similar for single and multiple administrations.
- An adequate treatment period is a minimum of 4 weeks in duration. Consider discontinuation if no response. For long-term use, treatment should be reviewed regularly to assess whether the number of plasters required can be reduced or the plaster-free period extended.
- Application to the head may be tolerated less well compared with the trunk and extremities.

Cautions

- Caution in patients with severe cardiac impairment, severe renal impairment or severe hepatic impairment.

Side effects

- The plaster contains propylene glycol which may cause skin irritation. It also contains methyl parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed). Approximately 16% of patients can be expected to experience adverse reactions. These are localised reactions due to the nature of the medicinal product.

Administration

- Cut plaster to size and shape of painful area. Do NOT use on broken or damaged skin or near the eyes. The plasters must be used within 14 days of opening the sachets.

Available as

- 700mg/medicated plaster (5% w/v lidocaine)

Evidence: (2,3,204–206)

Loperamide

Use:

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

Dose and routes for management of chronic diarrhoea

By mouth:

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

Notes

Licensing

- Not licensed for use in children with chronic diarrhoea. Capsules not licensed for use in children under 8 years. Syrup not licensed for use in children under 4 years.

Therapeutics

- Maximum therapeutic impact may not be seen for 16-24 hours.
- BNFc quotes a maximum of 2mg/kg/day in divided doses for children aged 1-11 months. However APPM has been unable to identify evidence of sufficient quality to justify this recommendation.
- Despite low bioavailability (due to almost complete first pass metabolism primarily by CYP3A4), some loperamide may be absorbed leading to life threatening toxicity in patients treated with very high doses, above the recommended maximum, for high output diarrhoeal or stoma losses

Side effects

- Constipation, nausea, flatulence.

Administration

- Orodispersible tablets can be dissolved in water. Disperse one orodispersible tablet in 4mL of water for a 0.5mg/mL suspension. For proportional doses, draw up the required dose and administer immediately. Resulting suspension can be administered without risk of blocking feeding tubes. Flush well after administration.
- Jejunal administration will not affect the therapeutic response to loperamide.

Patient information

- See Medicines for Children leaflet “Loperamide for diarrhoea” https://www.medicinesforchildren.org.uk/medicines/loperamide-for-diarrhoea/

Available as

- Tablets (2mg), capsules (2mg), orodispersible tablets (2mg).

Evidence: (1,2,8,207–209)

Lorazepam

Use

- Anxiety, including anxiety associated with dyspnoea
- Agitation and distress
- Adjuvant in cerebral irritation
- Muscle spasm
- Anticipatory nausea and vomiting in chemotherapy
- Status epilepticus

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Anxiety, agitation, cerebral irritability, muscle spasm, anticipatory nausea and vomiting

By mouth:

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

By buccal route:

- **Child 1 month and over**: 25micrograms/kg as a single dose, as required 2-3 times daily. Increase to 50micrograms/kg, maximum 1mg/dose, if necessary
- **Adult:** 500micrograms–1mg as a single dose, repeat as required.

Status epilepticus

By slow intravenous injection:

- **Neonate**: 100micrograms/kg/dose repeated after 10 minutes if required
- **Child 1 month-11 years**: 100micrograms/kg/dose, maximum 4mg, repeated after 10 minutes if required
- **12 years and over**: 4mg repeated after 10 minutes if required.

Notes

Licensing

- Licensed in children for status epilepticus. Tablets licensed in children over 5 years for premedication, injection not licensed in children less than 12 years except for treatment of status epilepticus.

Therapeutics

- Potency in the order of 10 times that of diazepam per mg as anxiolytic/sedative.

Cautions

- May cause drowsiness and respiratory depression if given in large dose. Half-life 10–20 hours therefore risk of accumulation with frequent PRN doses. Caution in renal and hepatic failure.

Pharmacokinetics

- Well absorbed buccally with rapid onset of effect. There may however be variable absorption by this route with further variation possible depending on the formulation used.

Administration

- Specific buccal tablets are not available in the UK but generic lorazepam tablets (specifically Genus, PVL or TEVA brands) do dissolve in the mouth so can be given buccally. Tablets may be dispersed in water for administration via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (250micrograms 500micrograms, 1mg, 2.5mg) and injection (4mg/ml), oral solution (1mg/ml: Licensed in UK but not licensed for use in children, expensive and contains significant quantity of ethanol as an excipient)

CD

- CD Schedule 4

Evidence: (1,3,8,87,87,122,158,210–213)

Macrogols

Use

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

Dose and route:

Constipation, prevention of opioid-induced constipation

By mouth

Using paediatric (or half adult-size) sachets for those less than 12 years of age

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

Using Movicol® liquid:

- **12 years and over**: 25 mL 1–3 times daily usually for up to 2 weeks; maintenance 25 ml 1–2 times daily.

Using Movicol® ready to take sachets:

- **12 years and over**: 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance 1–2 sachets daily.

Faecal impaction

By mouth:

Using paediatric (or half adult-size) sachets for those less than 12 years of age

- **Child under 1 year**: ½-1 paediatric sachet daily
- **Child 1-4 years**: 2 paediatric sachets on first day and increase by 2 sachets every 2 days (maximum 8 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy
- **Child 5-11 years**: 4 paediatric sachets on first day and increase by 2 sachets every 2 days (maximum 12 sachets daily). Treat until impaction resolved then switch to maintenance laxative therapy

- **12 years and over**: 4 adult sachets on first day, then increase by 2 sachets daily to a maximum of 8 adult sachets daily. Total daily dose should be drunk within a 6 hour period. After disimpaction switch to maintenance laxative therapy.

Notes

Osmotic laxative

Licensing

- Not licensed for use in children under 5 years with faecal impaction and under 2 years with chronic constipation.

Therapeutics

- Increased stool volume stimulates peristalsis, however no inherent stimulant action. Ensure adequate hydration.

Cautions

- Ready to take sachets have higher concentrations of electrolytes including sodium and potassium. Caution if fluid or electrolyte disturbance. Caution with high doses (volumes) in those with impaired gag reflex, reflux oesophagitis or impaired consciousness.

Administration

- Manufacturer advises dilute 25 ml of oral concentrate with 100 ml of water; after dilution the solution should be discarded if unused after 24 hours. Mix powder with water: follow manufacturers' instructions.
- For administration via a feeding tube: dissolve the powder (or liquid concentrate) in water as directed and flush down the feeding tube. Flush well after administration. Efficacy unlikely to be affected by jejunal administration

Patient information

- See Medicines for Children leaflet "Movicol for constipation" " https://www.medicinesforchildren.org.uk/medicines/movicol-for-constipation/

Available as

- Movicol and Movicol Paediatric Sachets, CosmoCol and CosmoCol Paediatric Sachets, Laxido and Laxido Paediatric Sachets, Macilax and Macilax Paediatric Sachets. Movicol is also available as an oral liquid concentrate (dilute with water before administration) and 25ml oral solution sachets.

Evidence: (1–3,8,214–216)

Melatonin

Use:

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

Dose and route:

By mouth:

- **Child 1 month and over**: 2–3mg at night, increasing every 1–2 weeks dependent on effectiveness up to maximum 10mg.

Notes:

Licensing

- Adaflex® immediate release tablets, Ceyesto® 3mg prolonged release tablets and Colonis® melatonin liquid 1mg/ml are licensed for treatment of insomnia in children with ADHD from 6 years of age. Slenyto® is licensed in children and adolescents aged 2-18 years with Autism Spectrum Disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. All other melatonin formulations are not licensed for use in children.

Therapeutics

- Treatment should be initiated by a specialist. Ensure appropriate attention to sleep hygiene. Some prescribers use a combination of immediate-release and modified release tablets to optimise sleep patterns.
- Maximum doses are frequently outside the individual product licences

Cautions

- Caution when switching between immediate-release formulations as the peak plasma melatonin concentration may be higher with the oral solution than with tablets. Intake with carbohydrate-rich meals may impair blood glucose control.
- Reduced clearance in hepatic impairment.

Interactions

- Metabolised by cytochrome P450 enzyme CYP1A2. Levels may be increased by drugs that inhibit this enzyme including ciprofloxacin. Levels may be reduced by drugs that induce this enzyme including phenytoin.

Administration

- Modified-release tablets should be taken with or after food. The modified-release tablet Slenyto® may be mixed whole into food or drink (e.g. yoghurt, orange juice, or ice-cream) immediately before administration. Licensed immediate-release formulations should be taken on an empty stomach, 2 hours before or 2 hours after food. The immediate-release tablet Adaflex® may be crushed and mixed with water immediately before administration. Use oral liquid for administration via an enteral feeding tube No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet: Melatonin for sleep disorders https://www.medicinesforchildren.org.uk/medicines/melatonin-for-sleep-disorders/

Available as

- Prolonged release mini-tablets 1mg, 5mg (Slenyto®), prolonged release tablets 2mg, 3mg (various), immediate release tablets 1mg, 2mg, 3mg, 4mg, 5mg (Adaflex®), oral solution 1mg/1ml (Colonis®)

Evidence:(1,2,8,217–221)

Methadone

Use:

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

Extremely important safety information

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

This is due to wide inter-individual variation in response, very variable conversion ratios with other opioids, complex pharmacokinetics and a long half-life.

Initial close monitoring is particularly important.

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in patients already receiving regular strong opioids

By mouth:

Convert using *specific protocols* from previous opioid analgesia

Caution: Converting a patient to methadone from another opioid analgesic is a specialist skill and should only be undertaken in close collaboration with practitioners experienced in its use. There is a risk of unexpected death through overdose.

Consider other opioids first before rotating from morphine to methadone due to unacceptable side effects or inadequate analgesia. Consultation with a pain clinic or specialist palliative care service is advised

It can be difficult to convert a short or long-acting opioid to an equivalent dose of methadone. Current practice is usually to admit to a specialist inpatient unit or titrate orally at home with very close supervision. Close monitoring should be continued for a period of two weeks.

Equianalgesic doses

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

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

Protocols for converting patients to methadone

In adults there are several protocols for converting patients to methadone. These are not evidence based in paediatrics.

- *The reduce-and-replace* (also known as 3-day switch) protocol incorporates a transition period where the dose of the former opioid is reduced and partially replaced by methadone. The methadone dose is then titrated upwards. This approach is considered safer and may be more effective.
- *The rapid-conversion* (also known as regular-dose or stop-and-go), protocol advocates stopping previous opioid therapy completely and then starting a fixed dose of methadone at regular intervals.

Reduce-and-replace protocol

1. Calculate the average total daily oral morphine equivalent (OME)

   Add up the patient's total oral opiate requirement over the previous 48 hours. Use the equianalgesic table (Appendix 1) to calculate the oral morphine equivalent (OME). Do not include breakthrough doses for incident pain. Divide by two to give the average total daily OME

2. Convert the average total daily OME to the approximate equianalgesic dose of methadone using the table below

Total daily OME	**Equianalgesic ratio morphine(mg):methadone(mg)** Divide by this ratio
Less than 90mg/day	4:1
90-299mg/day	6:1
300-599mg/day	8:1
600-799mg/day	12:1
800mg/day or more	15:1

3. Replace original opioid with methadone, stepwise over 3 days

   - *Day 1* replace 1/3 of original opioid with equianalgesic dose of methadone in 3 divided doses
   - *Day 2* replace 2/3 of original opioid with equianalgesic dose of methadone in 3 divided doses
   - *Day 3* onwards replace all of original opioid with equianalgesic dose of methadone in 3 divided doses

4. Consider reducing the dose of methadone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

   Example:

   Total daily OME = 900mg/day

   Equianalgesic ratio for total daily OME of 900mg/day = 15:1 (from the table above)

   Divide OME by equianalgesic ratio to obtain equianalgesic dose of methadone

   900mg/day OME ÷ 15/1 = 60mg methadone

   Reduce the dose of methadone by 50% as the patient is already on a high dose of the previous opioid

   60mg methadone x 50% = 30mg methadone

Day 1: Give 2/3 original opioid (OME 600mg) and 1/3 equianalgesic dose of methadone in 3 divided doses

= 30mg ÷ 3 = 10mg methadone in 3 divided doses

= 10mg methadone ÷ 3 = 3.3mg methadone three times daily

Day 2: Give 1/3 original opioid (OME 300mg) and 2/3 equianalgesic dose of methadone in 3 divided doses

= 30mg ÷ 3 = 10mg methadone in 3 divided doses

= 10mg methadone ÷ 3 x 2 = 6.6mg methadone three times daily

Day 3: Stop original opioid and give full equianalgesic dose of methadone in 3 divided doses

= 30mg ÷ 3 = 10mg methadone three times daily

5. Use an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain. It may also be necessary to reduce the breakthrough dose by 25-50%
6. Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may be required for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose may be sufficient.
7. To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 20% approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently). Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.
8. If excess sedation occurs reduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission

Rapid-conversion-protocol

1. Calculate the average total daily oral morphine equivalent (OME)

   Add up the patient's total oral opiate requirement over the previous 48 hours. Use the equianalgesic table (Appendix 1) to calculate the oral morphine equivalent (OME). Do not include breakthrough doses for incident pain. Divide by two to give the average total daily OME

2. Convert the adjusted total daily OME (from step 1 above) to the equianalgesic dose of oral methadone by dividing by 15 (most guides say 10 so this is a cautious approach).
3. Consider reducing the dose of methadone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation
4. Calculate the initial methadone dose by dividing the equianalgesic dose of methadone (from step 3 above) by 3.

   The initial dose would not normally exceed

- **Child body-weight less than 50kg**: 5mg three times daily
- **Body-weight 50kg and over**: 10mg three times daily

If converting from a long-acting opioid, give the first methadone dose 6 hours after the last long-acting opioid dose or 10-12 hours after opioid patch removal.

Example:

Total daily OME = 900mg/day

900mg/day OME ÷ 15 = 60mg methadone

Reduce the dose of methadone by 50% as the patient is already on a high dose of the previous opioid

60mg methadone x 50% = 30mg methadone

Calculate the initial methadone dose by dividing the equianalgesic dose of methadone by 3

= 30mg ÷3 = 10mg three times daily

5. Use an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain. It may also be necessary to reduce the breakthrough dose by 25-50%
6. Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may be required for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose may be sufficient.
7. To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 20% approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently). Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.
8. If excess sedation occurs reduce dose by 25-50% or omit dose. Sudden good analgesia can also indicate overdose and should trigger consideration of dose reduction or omission.

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

Convert from previous opioid analgesia using appropriate methadone conversion protocol if applicable

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose of oral methadone administered over the previous 24 hours

  Divide the total daily dose of oral methadone by two and administer by continuous infusion

  Ensure continued access to immediate release morphine as required for breakthrough pain

Alternatively, the total daily dose of intravenous or subcutaneous methadone can be given as a single intravenous bolus injection over 3-5minutes or 2-3 divided doses

Seek specialist guidance if mixing with any other drug.

Pain in opioid naïve patients

By mouth:

Opioid naive patients: the maximum dose stated applies to starting dose only

- **Child 1-12 years**: 50-100micrograms/kg/dose, maximum 2.5mg, 2-3 times daily
- **12 years and over**: 2.5mg/dose, 2–3 times daily

Methadone has a long and variable half-life with potential to cause sedation, respiratory depression and even death from secondary peak phenomenon.

Consider using an alternative short acting opioid (such as morphine oral solution) for management of breakthrough pain.

Titration of methadone dosing must be done under close clinical observation of the patient particularly in the first few days. Due to large volume of distribution, higher doses may be required for the first few days whilst body tissues become saturated. Once saturation is complete, a smaller dose may be sufficient.

To prevent adverse effects, increments in enteral dosing should be very cautious and usually by no more than 20% approximately at weekly intervals with a maximum increase of 50% (experienced practitioners may increase more frequently). Continued clinical reassessment is required to avoid toxicity as the time to reach steady state concentration following a change in dosing may be up to 12 days.

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

Notes:

- Strong opioid with μ-opioid receptor agonist, and NMDA-receptor–channel blocker properties

Licensing

- Not licensed for use in children.

Therapeutics

- Methadone is a racemic mixture: L-isomer, analgesic active (levomethadone; L-polamidon®); R-isomer unknown action.
- In some countries levomethadone is available. It has a different strength to methadone.
- Partial replacement of former opioid is sometimes used if completing the full switch produces intolerable adverse effects: however completing the switch rather than using a combination of opioids is recommended in the first instance
- A naloxone infusion should be used to treat methadone overdose in view of the long and variable half-life
- Respiratory depressant effects may last longer than analgesic effects.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Cautions

- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval

Monitoring

- Following concerns regarding methadone and sudden death from prolongation of QT-interval or Torsades de Pointes (especially at high doses) it is recommended that patients have an ECG prior to initiation of treatment and regularly whilst on methadone, particularly if they have any risk factors or are having intravenous treatment with methadone.

Side effects

- Usual strong opioid side effects.
- Also associated with prolonged QT-interval and ventricular arrhythmia (torsade de pointes)

Pharmacokinetics

- Limited data in paediatric patients; known to have wide inter-individual variation.
- Newer evidence suggests oral bioavailability may be as much as 80%

Hepatic impairment, renal impairment

- Reduce methadone dose by 50% in severe renal impairment and titrate according to response.
- Significant accumulation is unlikely in renal failure, as elimination is primarily via the liver.
- Avoid in severe hepatic impairment

Interactions

- Opioid antagonists naloxone and naltrexone will precipitate an acute withdrawal syndrome in methadone dependent patients. Naloxone will antagonise the analgesic, CNS and respiratory depressant effects of methadone.
- Metabolised by cytochrome P450 enzymes CYP2B6 and CYP3A4. Levels increased by drugs that inhibit these enzymes including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels may be reduced by drugs that induce these enzymes including carbamazepine, phenobarbital and phenytoin.

Administration

- If CSCI methadone causes a skin reaction, consider doubling the dilution and changing the syringe every 12 hours
- Use liquid preparations for administration via feeding tube. Absorption of methadone is unlikely to be affected by jejunal administration.

Available as

- Linctus (2mg/5ml), mixture (1mg/ml), oral solution (1mg/ml, 5mg/ml, 10mg/ml, and 20mg/ml), tablets (5mg), and injection (10mg/ml, 50mg/ml, 50mg/2 ml).

CD

- CD schedule 2.

Evidence: (2,3,8,10,120,120,222,222–233)

Methylnaltrexone

Use:

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

Dose and routes

By intermittent subcutaneous (or intravenous) bolus:

- **Child 1 month- 12 years or body weight less than 38kg**: 150micrograms/kg, maximum 8mg, as a single dose
- **Over 12 years, body-weight 38-61kg**: 8mg as a single dose
- **Over 12 years and body-weight over 61kg**: 12mg as a single dose

A single dose may be sufficient: repeat doses may be given with a usual administration schedule of a single dose every other day.

Doses may be given at longer intervals, as per clinical need.

Patients may receive 2 consecutive doses (24 hours apart) only when there has been no response (no bowel movement) to the dose on the preceding day.

Notes:

- 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.

Licensing

- Not licensed for use in children or adolescents less than 18 years. Licensed for subcutaneous but not intravenous administration in adults.

Therapeutics

- Constipation in palliative care is usually multifactorial and other laxatives are often required in addition: continue all other laxative treatment.
- May also improve other peripheral effects of opioids, e.g. delayed gastric emptying, urinary retention. Case reports also suggest benefit in cholestatic pruritus.
- Does not cross blood brain barrier.
- Onset of action may be within 15-60 minutes: 30-50% patients have a bowel movement within 4 hours, without loss of analgesia.
- Has been used orally in adults, using a specially formulated tablet preparation, at doses of up to 450mg daily

Contraindications, cautions

- Contraindicated in known or suspected bowel obstruction other than that caused by opiate-induced constipation.

Side effects

- Common: abdominal pain/colic, diarrhoea, flatulence and nausea.

Renal impairment

- Reduce dose by 50% in severe renal impairment.

Administration

- Rotate the site of subcutaneous injection. Do not inject into areas where the skin is tender, bruised, red or hard.

Available as

- Single use vial 12mg/0.6ml solution for SC injection (Relistor®)

Evidence: (2,3,216,234–237)

Metoclopramide

Use

- Prokinetic anti-emetic, in gastric compression or gastroparesis
- Hiccups

Dose and route:

By mouth, intramuscular, subcutaneous or slow intravenous injection

- **Child 1-18 years**: 100-150 microgram/kg repeated up to 3 times daily. The maximum dose in 24 hours is 500 microgram/kg (maximum 10 mg/dose; 30 mg daily).

Total daily dose may be administered as a continuous subcutaneous or intravenous infusion/24hours

Notes:

Licensing

- Not licensed for use in infants less than 1 year of age. Tablets not licensed for use in under 15 years (body-weight less than 61 kg). Not licensed for continuous infusion.

Therapeutics

- Efficacy comparable to domperidone in gastroparesis but higher incidence of adverse effects
- Use in palliative care only when alternative treatments do not work or cannot be used.
- Treatment should be limited to short term use (up to 5 days) if at all possible
- Has also been used in refractory hiccup not responsive to physical measures, or first line medication

Contraindications, cautions

- Contraindicated in children younger than 1 year, except in palliative care where no other alternative is available.
- Epilepsy: increased frequency and severity of epileptic seizures
- The EMA (2013) recommends that, due to the risk of neurological side effects, metoclopramide should only be used in children aged 1-18 as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting, and for treatment of established postoperative nausea and vomiting, and only when other treatments do not work or cannot be used.

Side effects

- Acute dystonic reactions including muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. Dystonic effects usually occur shortly after starting treatment and subside within 24 hours of discontinuation. Acute dystonic reactions can be effectively reversed using anticholinergics e.g. procyclidine and/or benzodiazepines e.g. diazepam.
- Neuroleptic malignant syndrome
- Risk of extrapyramidal effects is dose related and increased with co-administration of other drugs known to cause extrapyramidal effects

Administration

- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.
- Oral liquid formulations should be given via a graduated oral syringe to ensure dose accuracy in children. The oral liquid may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.

Available as

- Tablets (10mg), oral solution (5mg/5ml) and injection (5mg/ml).

Evidence: (1,2,8,238–240)

Metronidazole topically

Use:

- Reduction of odour caused by anaerobic bacteria associated with wounds or fungating tumours

Dose and route:

By topical application:

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

Notes:

Licensing

- Off label use. Anabact® not licensed for use in children under 12 years.
- Metrogel® not licensed for use with children.

Administration

- Avoid eye area due to stinging.

Available as

- Cream and gel (Anabact® 0.75%, Metrogel® 0.75%).

Evidence: (1,2,241,242)

Miconazole oral gel

Use:

• Oral and intestinal fungal infection.

Dose and route:

Prevention and treatment of oral candidiasis

By mouth:

- **Neonate**: 1ml 2-4 times daily smeared around inside of mouth after feeds.
- **Child 1- 23 months**: 1.25 ml 4 times daily smeared around inside of mouth after food
- **Child 2 years and over:** 2.5 ml 4 times daily after meals

Continue treatment for at least 7 days after lesions have healed or symptoms have disappeared.

Prevention and treatment of intestinal candidiasis

By mouth:

- **Child 4 months and over**: 5mg/kg 4 times daily; max. 250mg (approximately 10 ml) 4 times daily.

Notes:

Licensing

- Not licensed for use in children under 4 months or during the first 5-6 months of life of an infant born preterm.
- Muco-adhesive tablet licensed in USA for child over 16 years.

Contraindications, cautions

- Contraindicated in infants with impaired swallow.

Interactions

- Increased INR/ bleeding has been reported with concomitant use of buccal miconazole and oral anticoagulants.

Administration

- Avoid applying near the back of the throat in infants and babies due to choking risk
- Retain in the mouth near lesions for as long as possible before swallowing.
- 50mg muco-adhesive buccal tablets should be applied to the upper gum just above the incisor tooth once daily for 7-14 days.
- Orthodontic appliances should be removed at night and brushed with gel.

Available as

- Oral gel (20mg per gram or 124mg per 5ml approximately 24mg/ml) in 15g and 80g tube, orange flavour. 15g oral gel can be brought over the counter

- A muco-adhesive buccal tablet of miconazole is now available. Indicated for the treatment of oropharyngeal candidiasis in immunocompromised adults, Loramyc®

Evidence: (1,2)

Midazolam

Use:

- Status epilepticus and terminal seizure control.
- Conscious sedation for procedures, to minimise awareness in terminal haemorrhage
- Management of anxiety/agitation associated with symptoms at the end of life.
- Anxiety associated with dyspnoea.
- Adjuvant for pain of cerebral irritation.
- Dystonia rescue

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Status epilepticus

<table>
<tr><th></th><th>By buccal or intranasal route:</th><th>By subcutaneous or slow intravenous bolus injection</th><th rowspan="2">By continuous intravenous or subcutaneous infusion for seizure control at end of life</th></tr>
<tr><td colspan="2">Doses can be repeated once after an interval of at least 10 minutes</td></tr>
<tr><td>Neonate</td><td>300microgram/kg, maximum 1.25mg/dose</td><td rowspan="6">200micrograms/kg/dose maximum 10mg/dose</td><td>1mg/kg/24hours
increasing gradually to a maximum of 7mg/kg/24hours</td></tr>
<tr><td>Child 1-2 months</td><td>300microgram/kg, maximum 2.5mg/dose</td><td rowspan="5">1mg/kg/24hours
Increasing gradually to a maximum of 7mg/kg/24hours, maximum 60mg/24hours

Higher doses up to 150mg/24hours have been used. Seek specialist advice, and consider addition of other agents such as phenobarbital before increasing above 60mg/24hours.</td></tr>
<tr><td>3-11 months</td><td>2.5mg/dose</td></tr>
<tr><td>1-4 years:</td><td>5mg/dose</td></tr>
<tr><td>5-9 years:</td><td>7.5mg/dose</td></tr>
<tr><td>10 years and over</td><td>10mg/dose</td></tr>
</table>

Conscious sedation e.g. for procedures, or to minimise awareness in terminal haemorrhage

Doses can be repeated once after an interval of at least 10 minutes

<table>
<tr><th></th><th>By buccal or intranasal route:</th><th>By subcutaneous or slow intravenous bolus injection</th><th>By mouth</th></tr>
<tr><td>Neonate</td><td>300microgram/kg, maximum 1.25mg/dose</td><td rowspan="6">200micrograms/kg/dose maximum 10mg/dose</td><td rowspan="6">500micrograms/kg/dose maximum 20mg</td></tr>
<tr><td>Child 1-2 months</td><td>300microgram/kg, maximum 2.5mg/dose</td></tr>
<tr><td>3-11 months</td><td>2.5mg/dose</td></tr>
<tr><td>1-4 years</td><td>5mg/dose</td></tr>
<tr><td>5-9 years</td><td>7.5mg/dose</td></tr>
<tr><td>10 years and over</td><td>10mg/dose</td></tr>
</table>

Anxiety, agitation at end of life, cerebral irritation, dystonia rescue

Doses refer to ***starting*** doses only

Age range[a]	Buccal[b]	Oral[c]	Intravenous or subcutaneous bolus[d]	Continuous intravenous or subcutaneous infusion[e]
Neonate	75microgram/kg Initial maximum 300micrograms/dose As required 6 -8 hourly, maximum 2 hourly	150micrograms/kg Initial maximum 600micrograms/dose As required 6 -8 hourly, maximum 2 hourly	50micrograms/kg Initial maximum 200micrograms/dose As required 6 -8 hourly, maximum 2 hourly	200micrograms/kg /24hours Initial maximum 800micrograms/24hours
1-2 months (less than 5.5kg)	75microgram/kg Initial maximum 500micrograms/dose As required 4-6 hourly, maximum hourly	150micrograms/kg Initial maximum 1mg/dose As required 4-6 hourly, maximum hourly	50micrograms/kg Initial maximum 300micrograms/dose As required 4-6 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 1.2mg/24hours
3-11 months (5.6-9.9kg)	500micrograms-1mg As required 4 hourly, maximum hourly	1.5mg As required 4 hourly, maximum hourly	50micrograms/kg Initial maximum 500micrograms/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 2mg/24hours
1-4 years (10-17kg)	1.5mg As required 4 hourly, maximum hourly	2.5mg As required 4 hourly, maximum hourly	50micrograms/kg Initial maximum 1mg/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 4mg/24hours
5-9 years (18kg-32kg)	2mg As required 4 hourly, maximum hourly	3.5mg As required 4 hourly, maximum hourly	50micrograms/kg Initial maximum 1.5mg/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 6mg/24hours
10 years and over (over 32kg)	2.5mg As required 4 hourly, maximum hourly	5mg As required 4 hourly, maximum hourly	50microgram/kg Initial maximum 2.5mg/dose As required 4 hourly, maximum hourly	200micrograms/kg over 24hours Initial maximum 10mg/24hours

[a] Aged based doses rounded to nearest 500micrograms for convenience of administration
[b] Based on 25% buccal seizure rescue dose
[c] Based on buccal bioavailability of 75% and oral bioavailability of 40%
[d] Based on 25% intravenous / subcutaneous seizure rescue dose
[e] Based on 4 x intravenous/subcutaneous dose for anxiety, agitation, breathlessness

Notes

Licensing

- The range of potential indications for midazolam in paediatric palliative care is very wide, but most are not licensed in infants or in children. See product literature.
- Oromucosal solution licensed only for seizure control in children 3 months of age and over. Midazolam injection is not licensed for oral or buccal administration. Midazolam injection licensed only for procedural sedation, anaesthesia and sedation in intensive care.

Therapeutics

- Doses above derived from standard doses for epilepsy via buccal and intravenous routes, taking into account recommendations in adult palliative care, and available information on bioavailability and pharmacokinetics in neonates, children and adults
- Dose recommendations in adult palliative care have been reduced over time due to recognition that lower doses were as effective and resulted in fewer adverse effects. Dose recommendations take this into account however it is important to recognise that the population of patients receiving palliative care in the adult sector is not typical of the paediatric palliative care population
- Pharmacology in children is complex and not well understood. Clearance is increased in sick patients particularly those ventilated on PICU. Tolerance/clearance may be higher in young adult males and in those already receiving other benzodiazepines and other drugs that may increase metabolism. If in doubt, start at the lowest recommended dose and titrate rapidly.
- In single dose for seizures, buccal midazolam is twice as potent as rectal diazepam. For patients who usually receive rectal diazepam for management of status, consider an initial dose of buccal midazolam that is 50% of their usual rectal diazepam dose to minimise the risk of respiratory depression
- Patients receiving midazolam by continuous infusion should continue to have buccal and/or bolus midazolam available as required for breakthrough symptoms. The background infusion can then be increased, no more often than every 12 hours, taking into account the requirement for breakthrough doses.
- Alternatively midazolam can be administered as a continuous patient controlled, patient-proxy controlled or nurse controlled infusion starting with a bolus dose equivalent to the hourly background rate and a lockout of between 5 and 15 minutes.
- Consider adding in an antipsychotic e.g. levomepromazine, before increasing midazolam above 600micrograms/kg/24hours or 30mg/24hours in agitation at end of life.

Cautions

- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency.

Side effects

- Both high and low doses can lead to paradoxical agitation.

Pharmacokinetics

- Buccal bioavailability will be lower if some of the dose is swallowed: this is more likely when used for indications other than status epilepticus, or larger volumes
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 minutes. Half-life 2-5 hours.
- Onset of action by oral or gastrostomy route 10-30 minutes.
- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Half-life may be shorter in patients on enzyme inducing drugs or those already receiving benzodiazepines

- Repeated dosing within an hour leads to increased peak and AUC (area under the plasma drug concentration-time curve)
- Half-life in neonates may be longer due to hepatic immaturity
- Half-life may be much longer in sick patients especially those with multi-organ system failure or critically ill on intensive care, and obese patients

Interactions

- Metabolised by cytochrome P450 enzyme CYP3A4. Levels increased by inhibitors of this enzyme including aprepitant, ciprofloxacin, erythromycin and fluconazole. Levels reduced by inducers of this enzyme including carbamazepine, phenobarbital and phenytoin
- Fatalities have occurred after concurrent administration with higher than approved doses of olanzapine
- The addition of a CYP3A4 inducer may reduce midazolam levels by ≤90%. Use of a different benzodiazepine is recommended if a moderate or potent inducer is essential
- Plasma concentrations of midazolam can be eight times higher after the addition of a CYP3A4 inhibitor. Midazolam doses may need to be reduced by ≥50%.

Administration

- For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Anecdotal reports of oral solution or injection administered via buccal route
- If enteral tube administration is indicated, the oral liquid or injection can be used.

Patient information

- See Medicines for Children leaflet “Midazolam for stopping seizures” https://www.medicinesforchildren.org.uk/medicines/midazolam-for-stopping-seizures/

Available as

- *Injection* (1mg/ml, 2mg/ml and 5mg/ml). *Oral solution* (5mg/ml Miprosed® and Thame generic and 2mg/ml Ozalin®). *Buccal liquid* Pre-filled oral syringes (strength 5mg/ml) available as 10mg in 2ml, 7.5mg in 1.5ml, 5mg in 1ml and 2.5mg in 0.5ml (e.g. Buccolam®, generics). Pre-filled oral syringes (strength 10mg/ml) available as 10mg in 1ml, 7.5mg in 0.75ml, 5mg in 0.5ml and 2.5mg in 0.25ml (e.g. Epistatus)
- Epistatus is also available as an unlicensed special in a 5ml multidose bottle (strength 10mg/ml) which is very useful when small doses are required
- Other oral and buccal liquids may also be available from ‘specials’ manufacturers or specialist importing companies (unlicensed)
- The buccal and oral formulations available differ in strengths-take care with prescribing and administration

CD

- CD Schedule 3 (CD No Register). Local protocols may require safe storage..

Evidence: (1–3,8,11,243–248)

Morphine

Use:

- Moderate to severe pain.
- Dyspnoea.

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in opioid naïve patients

Doses refer to ***starting*** doses only[a]

Age range	By mouth or per rectum	Intravenous or subcutaneous bolus	Intravenous or subcutaneous infusion/24hours
Neonate	80micrograms/kg/dose 6 hourly	40micrograms/kg/dose 6 hourly	160micrograms/kg/24hours
Child 1-2 months	120micrograms/kg/dose 6 hourly	60micrograms/kg/dose 6 hourly	240micrograms/kg/24hours
3-5 months	120micrograms/kg/dose 4 hourly	60micrograms/kg/dose 4 hourly	360micrograms/kg/24hours
6-23 months	200micrograms/kg/dose 4 hourly	80micrograms/kg/dose 4 hourly	480micrograms/kg/24hours
2-11 years	200-300micrograms/kg/dose maximum 10mg/dose 4 hourly	80-100micrograms/kg/dose maximum 5mg/dose 4 hourly	480-600micrograms/kg/24hours maximum 20mg/24hours
12 years and over	200micrograms/kg/dose maximum 10mg/dose 4 hourly *Alternatively* 5-10mg/dose, 4 hourly	80-100micrograms/kg/dose maximum 5mg/dose 4 hourly *Alternatively* 2.5-5mg/dose, 4 hourly	480-600micrograms/kg/24hours maximum 30mg/24hours *Alternatively* 20-30mg/24hours

Pain in patients already receiving regular strong opioids

Convert using oral morphine equivalent (OME) from previous opioid analgesia, if applicable, see Appendix 1

By mouth using modified release preparations

- Calculate the total daily dose (regular + PRN) of oral morphine administered over the previous 24 hours once the patient is established on regular morphine for 2-3 days

  12 hourly preparations: Divide the total daily dose of oral morphine by two and administer every 12 hours

  24 hourly preparations: Administer the total daily dose of oral morphine every 24 hours

  Ensure continued access to immediate release morphine as required for breakthrough pain see below

[a] Doses derived from primary research and cross referenced to BNFc ensuring age bands and dosing intervals are consistent, taking into account longer half-life in neonates and infants, equianalgesia, bio-availability via different routes, and ensuring consistent total daily dose across each age band

By continuous intravenous or subcutaneous infusion

- Calculate the total daily dose (regular + PRN) of oral morphine administered over the previous 24 hours

  Divide the total daily dose of oral morphine by ***three*** and administer by continuous infusion

  Ensure continued access to immediate release morphine as required for breakthrough pain see below

Breakthrough Pain in patients already receiving regular strong opioids

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10 to 1/6 of total daily morphine dose every 1-4 hours as required.
- Remember to convert dose If a different route is used for breakthrough and background e.g. CSCI with oral for breakthrough

  Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

Dyspnoea, cough suppressant

By mouth, subcutaneous or intravenous routes

- **Child 1 month and over:** 25-50% of pain doses

Notes:

- Strong opiate of first choice by mouth and for intravenous or continuous subcutaneous infusion

Licensing

- Oramorph® solution and MXL® capsules not licensed for use in children aged under 1 year. Sevredol ® tablets not licensed for use in children under 3 years. MST Continus® preparations licensed to treat children with cancer pain (age-range not specified by manufacturer). Actimorph® orodispersible tablets not licensed for use in children under 6 months.

Therapeutics

- Systematic review evidence suggests an equianalgesic oral to intravenous ratio of to 3:1 may be more appropriate than previously recommended ratio of 2:1.
- Some adult centres advocate giving patients on regular immediate release morphine a double dose of morphine immediate release at bed-time. This appears to be safe and reduces the likelihood of the patient waking overnight in pain.
- Can be used as a cough suppressant when treating the underlying cause is either not helpful or not possible and when other measures e.g. demulcents are not effective.
- Use ideal body weight (Appendix 7) when calculating doses in obese children
- In some circumstances, particularly opioid naïve patients at increased risk of adverse effects, it may be appropriate to start at lower doses, between $^{1}/_{10}$ and ½ of those quoted above, titrating according to response.

- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Cautions

- Caution in renal or hepatic impairment. Reduce dose and/or interval frequency. Avoid in severe
- renal impairment
- Avoid rectal administration in children with low platelets and/or neutropaenia.

Side effects

- Usual opioid side effects. Children may have a higher incidence of pruritus and urinary retention
- Toxicity often presents as myoclonic twitching.

Pharmacokinetics

- Oral absorption more variable and may be higher in neonates
- Orodispersible tablets are dissolved orally and swallowed: no significant buccal or sublingual absorption
- Higher volume of distribution in preterm and neonates especially days 2-5
- Converted to active metabolites by liver then excreted by kidneys: maturation to adult pharmacokinetics by approximately 6 months
- Clearance of morphine in some younger children may be higher than adults
- Some evidence suggests that area under time-concentration curve may be lower for subcutaneous rather than intravenous infusions. However APPM recommendation is to assume similar pharmacokinetics for intravenous and subcutaneous dosing.

Administration

- Oral solution can be administered undiluted via gastrostomy tube. Dilute with an equal volume of water for administration via a jejunostomy. Flush well to ensure total dose is delivered.
- Zomorph capsules can be opened to release the granules. The granules should not be crushed. Part doses should not be given as accuracy cannot be established. Zomorph granules can mixed with water for administration via an enteral feeding tube. The granules settle quickly in the syringe and care must be taken to deliver the complete dose. Zomorph granules can be administered via a 16Fr and above gastrostomy. Administration tubes as small as 8Fr without blockage has been reported. Caution would be advised in tubes of small diameter and a plan for unblocking the tube should be in place.
- MXL capsules can be opened and sprinkled on to food but are ***not*** suitable for administration via a feeding tube
- Morphine slow release tablets can be administered rectally.

Patient information

- See Medicines for Children leaflet “Morphine for pain” https://www.medicinesforchildren.org.uk/medicines/morphine-for-pain/

Available as

- *Tablets* (10mg-can be halved, 20mg, 50mg). Also available as *orodispersible tablets* (Actimorph®) 1mg, 2.5mg, 5mg, 10mg, 20mg, 30mg. Tablets should be placed on the tongue, and allowed to disperse before swallowing. Alternatively, tablets can be placed in a spoon and dispersed in a small amount of water before administration.
- *Oral solution* 10mg/5ml (Oramorph*)*, concentrated oral solution 100mg/5ml. An unlicensed lower strength oral solution 100micrograms/1ml is available from UK ‘specials’ manufacturers for accurate measurement of small doses especially in neonates.

- *Modified release tablets and capsules* Tablets12-hourly (5mg, 10mg, 15mg, 30mg, 60mg, 100mg, 200mg), modified release capsules 12-hourly (ZOMORPH 10mg, 30mg, 60mg, 100mg, 200mg), modified release capsules 24-hourly (30mg, 60mg, 90mg, 120mg, 150mg, 200mg).
- *Suppositories* (10mg): other strengths may be available from specials manufacturers.
- *Injection* (1mg/ml, 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml).

CD

- CD Schedule 2 except morphine oral solution10mg/5ml and neonatal morphine solution 100micograms/ml

Evidence: (1–3,8,11,61,62,115,117,249)

Nabilone

Use:

- Nausea and vomiting caused by cytotoxic chemotherapy (not first or second line therapy).
- Nausea and vomiting unresponsive to conventional antiemetics.
- Management of upper gastrointestinal symptoms in gut dystonia.

Dose and route:

By mouth:

- **Child less than 18 kg**: 500micrograms twice daily
- **Child 18- 30 kg**: 1mg twice daily
- **Child over 30 kg**: 1mg three times daily
- **Adult:** 1–2mg twice daily (maximum dose 6mg/day in 2-3 divided doses)

Notes:

- Synthetic cannabinoid.

Licensing

- Not licensed for use in children.

Therapeutics

- Specialist use only. Response varies between patients requiring close medical supervision on commencement and dose adjustments. Effects may persist for a variable and unpredictable period of time following oral administration.

Side effects

- Somnolence, dizziness and abdominal pain
- Adverse psychiatric reactions can persist for 48-72 hours following cessation of treatment.
- Decreased or increased appetite

Hepatic impairment, renal impairment

- Avoid in severe hepatic impairment.

Administration

- No information available regarding administration via enteral feeding tubes

Available as

- Capsules (250 micrograms, 1mg).

CD

- Schedule 2 CD.

Evidence: (1–3,250,251)

Naloxone

Use:

- Emergency reversal of life threatening opioid-induced respiratory depression or opioid overdose.

Dose and route:

Partial reversal of respiratory depression due to acute opioid overdose

When there is risk of acute opioid withdrawal or when a continued therapeutic effect is required

By intravenous injection:

Doses approximately equal to twice the intravenous dose can be given subcutaneously or intramuscularly if intravenous access is not available, but slower onset of action

- **Neonate, child 1 month-11 years**: 1–10micrograms/kg, maximum 200micrograms per dose

  Then, if no response, repeat at intervals of 1 minute up to 5 times

  Then, if still no response, single dose of 100micrograms/kg (maximum dose 2mg)

- **12 years and over:** 100–200micrograms per dose

  Then, if no response, 100micrograms at 1 minute intervals for up to 2 doses

  Then, if still no response continue titrating up to a maximum of 2mg per dose

- If still no response, give a further 2mg dose: 4mg dose may be required in seriously compromised patients

Review diagnosis if still no response. Further doses, or infusion, may be required if respiratory function deteriorates following initial response.

By continuous intravenous infusion

Continued partial reversal of respiratory depression due to acute opioid overdose e.g. for long acting opioids

- 60% of the initial effective dose per hour, rate adjusted according to response

  Initial effective dose is that which maintained satisfactory self-ventilation for 15 minutes.

Complete reversal of respiratory depression due to acute opioid overdose

By intravenous injection:

Doses approximately equal to twice the intravenous dose can be given subcutaneously or intramuscularly if intravenous access is not available, but slower onset of action

- **Neonate, child 1 month-11 years**: 100micrograms/kg.

  Then, if no response repeat at intervals of 1 minute to a maximum of 2mg

- **12 years and over:** initially 400micrograms.

Then, if no response, 800micrograms at 1 minute intervals for up to 2 doses

Then, if still no response, 2mg for 1 dose: 4mg dose may be required in seriously compromised patients.

Further doses, or infusion, may be required if respiratory depression deteriorates following initial response

By intranasal route

- **Child body-weight 9kg and over:** 1.8 mg, administered into one nostril

  Repeat dose into alternate nostril if no response after 2-3 minutes.

  Repeat dose immediately if initial response is followed by further respiratory depression. Administer into alternate nostrils.

By continuous intravenous infusion

Continued complete reversal of respiratory depression due to acute opioid overdose e.g. for long acting opioids

- 60% of the initial resuscitative dose per hour, rate adjusted according to response

  Initial resuscitative dose is that which maintained satisfactory self-ventilation for 15 minutes.

Notes

- Potent opioid antagonist.

Licensing

- Intranasal spray not licensed for children below 14 years; limited experience in children.

Therapeutics

- In some circumstances temporary discontinuation of strong opioids together with close observation may be sufficient, rather than proceeding immediately to opioid reversal
- May have a role in reversal of clonidine toxicity.

Side effects

- Arrhythmias, dizziness, headache, hypertension, hypotension, nausea and vomiting.

Pharmacokinetics

- Short duration of action; repeated doses or infusion may be necessary to reverse effects of opioids with longer duration of action.
- Naloxone acts within 2 minutes of IV injection and within 3-5 minutes of SC or IM injection.
- Intranasal bioavailability approximately 50% *depending on formulation*

Available as

- Injection (20micrograms/ml, 400micrograms/ml, 21mg/2ml) and nasal spray 1.8m/0.1ml.

Evidence: (1,2,104,252–258)

Naproxen

Use:

- Non-steroidal anti-inflammatory analgesic
- Relief of symptoms in inflammatory arthritis and treatment of acute musculoskeletal syndromes

Dose and route:

By mouth

- **Child 2 years and over**: 5-7.5mg/kg/dose twice daily (maximum 1g/ day)

  Doses up to 10mg/kg twice daily (not exceeding 1g daily) have been used. Use the lowest effective dose for the shortest treatment duration possible.

Notes:

Licensing

- Licensed for use from 5 years of age for juvenile idiopathic arthritis; not licensed for use in children less than 16 years for other conditions.

Therapeutics

- Generally regarded as combining good efficacy with a low incidence of side effects.
- Anti-pyretic and anti-inflammatory actions may reduce fever and inflammation therefore reducing their utility as diagnostic signs.

Contraindications, cautions

- Contraindicated in patients with a history of hypersensitivity to any NSAID or in those with a coagulation disorder.
- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure

Side effects

- All NSAID use can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.
- All NSAIDs are associated with serious gastro-intestinal toxicity. Naproxen is associated with an intermediate risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.

Hepatic impairment, renal impairment

- Use with caution in renal, cardiac or hepatic failure as this may cause a deterioration in renal function; the dose should be kept as low as possible and renal function monitored. Avoid in GFR <20ml/min/1.73m2 and in those with severe hepatic or cardiac failure.

Administration

- For administration via an enteral feeding tube, using the oral suspension or effervescent tablets. Enteric coated naproxen tablets should be swallowed whole and NOT be crushed or chewed. Naproxen should be taken with or after food.

Available as

- Tablets 250mg and 500mg; effervescent tablets 250mg; enteric coated tablets 250mg, 375mg and 500mg; oral suspension 125mg/5ml, 25mg/ml, 50mg/ml.

Evidence: (1–3,8)

Nitrous oxide (Entonox®)

Use:

- As self-regulated analgesia without loss of consciousness e.g. painful dressing changes
- Not suitable for use outside of an acute healthcare setting

Dose and route:

By inhalation:

- **Child 2 years and over**: Up to 50% to be administered using suitable anaesthetic apparatus in oxygen adjusted according to the patient's needs. Self-regulated use usually over 5 years of age.

Notes:

Therapeutics

- Normally used as a light anaesthetic. Rapid onset and then offset.
- Training, governance and supply implications may limit application in hospice settings.

Contraindications, cautions

- Contraindicated in the presence of pneumothorax or intracranial air after head injury.

Side effects

- Risk of hypoxia immediately after administration: administer supplementary oxygen for several minutes following administration.
- Prolonged exposure (including environmental exposure to relatives) by continuous or intermittent administration may result in megaloblastic anaemia. Consider assessment of plasma vitamin B12 concentration. Depression of white cell formation may also occur. Neurological toxicity may occur without preceding overt haematological changes.
- Consider assessment of plasma vitamin B12 concentration in children at risk of deficiency.

Interactions

- Avoid concomitant use with methotrexate: increased antifolate effect.
- Risk of enhanced hypotensive effect with a number of medications.

Administration

- Should only be used as self-administration using a demand valve; all other situations require a specialist paediatric anaesthetist.

Patient information

- See Medicines for Children leaflet "Nitrous oxide for pain" https://www.medicinesforchildren.org.uk/medicines/nitrous-oxide-for-pain/

Available as

- Nitrous oxide 1ml per 1ml various sizes of cylinders available from medical gas suppliers Linde Gas UK and BOC Ltd. See BNFC for additional information.

Evidence: (1,259–261)

Nystatin

Use:

- Oral and perioral fungal infection.

Dose and route:

By mouth:

- **Neonate**: 100,000 units 4 times daily
- **Child 1-23 months**: 100,000-200,000 units 4 times daily
- **2 years and over:** 100,000-600,000 units 4 times daily

Notes:

Licensing

- Licensed for use in all ages. Licensed for prophylaxis against oral candidiasis in neonates at a dose of 1ml daily.

Therapeutics

- Treatment for 7 days and should be continued for 48 hours after lesions have healed.
- Higher doses allow greater mucosal contact and may therefore be more effective.

Administration

- Retain near lesions before swallowing.

Side effects

- Abdominal discomfort; angioedema; diarrhoea; facial oedema; nausea; sensitisation; skin reactions; Stevens-Johnson syndrome; vomiting
- Administer after food or feeds. If possible divide the dose between both sides of the mouth.

Available as

- Oral suspension 100,000 units/ml, 30ml with pipette.

Evidence: (1–3)

Octreotide

Use:

- Bleeding from oesophageal or gastric varices.
- Nausea and vomiting.
- Inoperable intestinal obstruction.
- Intractable diarrhoea.
- Hormone secreting tumours, ascites, bronchorrhoea.
- Chylothorax
- Hyperinsulaemic hypoglycaemia (specialist use)

Dose and route:

Gastrointestinal bleeding, chylothorax (NEW)

By continuous intravenous or subcutaneous infusion

- **Child 1 month and over**: 1microgram/kg/*hour*

  Higher doses may be required initially and for chylothorax. Usual maximum dose is 50micrograms/*hour*

  Reduce dose gradually over 24hours once there is no active bleeding.

Antiemetic, antisecretory, intractable diarrhoea, intestinal obstruction

By continuous intravenous or subcutaneous infusion

- **Child 1 month and over**: 5-10micrograms/kg/24hours. Usual maximum 750microgams/24hours

  Doses up to 30micrograms/kg/24hours may be required in intractable diarrhoea.

Hyperinsulaemic hypoglycaemia unresponsive to diazoxide and glucose (specialist use) (NEW)

By subcutaneous injection

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

Notes:

- Synthetic somatostatin analogue

Licensing

- Not licensed for use in children.

Therapeutics

- Acts as an inhibitory hormone throughout the body but particularly the gastro-enterohepatic system, increasing water and electrolyte absorption.
- Avoid abrupt withdrawal: may be associated with biliary colic and pancreatitis.
- May impair glucose tolerance: consider monitoring blood glucose.
- Rotate injection sites

Administration

- Dilute with sodium chloride 0.9% for intravenous injection and intravenous or subcutaneous infusion. Check the manufacturer's recommendations regarding dilution. Subcutaneous bolus injections may be administered undiluted but this can be painful (this can be reduced if the ampoule is warmed in the hand to body temperature before injection).

Available as

- Injection for subcutaneous or intravenous administration (50micrograms/ml, 100micrograms/ml, 200micrograms/ml, 500micrograms/ml, 1mg/5ml). Also available as depot injection for intramuscular administration every 28 days (10mg, 20mg and 30mg SandostatinLar®).

Evidence: (1–3,262–265)

Olanzapine

Use:

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

Dose and route:

Psychoses, mania

By mouth

- **Child under 12 years and up to 25kg**: Initial dose 2.5mg at night
- **Child under 12 years and greater than 25kg**: Initial dose 2.5-5mg at night.
- **12 years and over**: initial dose 5mg at night.

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

Agitation, delirium

By mouth

- **Child under 12 years**: Initial dose 1.25mg at night and as required,
- **12 years and over**: Initial dose 2.5mg at night and as required.

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

Nausea and vomiting, anorexia

- **Child under 12 years**: Initial dose 1.25mg (or 625micrograms if 2.5mg tablets can be cut into quarters) at night and as required
- **12 years and over**: Initial dose 1.25mg-2.5mg at night and as required.

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

Notes:

- Atypical (second generation) antipsychotic agent and antagonist of dopamine D1, D2, D4, 5-HT2, histamine-1-, and muscarinic-receptors.

Licensing

- Not licensed for use in children and adolescents less than 18 years of age although there is general acknowledgement of ‘off-label’ use in adolescents for the treatment of psychosis and schizophrenia and mania associated with bipolar disorder.
- Use in the treatment of agitation, delirium, nausea and vomiting and anorexia in palliative care are all ‘off-label’ indications.

Therapeutics

- Five times greater affinity for $5HT_2$ receptors than for D2 receptors, resulting in fewer extrapyramidal side effects.
- Activity at multiple receptors is similar to levomepromazine.
- Titrate dose slowly to minimise sedation.
- Adolescents may be more susceptible to weight gain
- Elevated lipid and prolactin levels. Consider monitoring before and during long term use
- Onset of action is hours-days in delirium; days-weeks in psychoses.

Contraindications, cautions

- Caution in cardiovascular disease. Caution in epilepsy and conditions predisposing to seizures: lowers seizure threshold

Side effects

- Very common (> 10% patients) side effects: weight gain; elevated triglyceride levels; increased appetite; sedation; increased ALT and AST levels; decreased bilirubin; increased GGT and plasma prolactin levels. Common (1-10% patients) side effects: elevated cholesterol levels; dry mouth.
- Rare but potentially serious adverse effects include neuroleptic malignant syndrome, cardiovascular disease, severe respiratory disease and bone marrow depression, hepatitis, pancreatitis and hyperglycaemia.

Hepatic impairment, renal impairment

- Consider lower starting dose (maximum 5mg in adults) in patients with renal and/or hepatic impairment.

Interactions

- Metabolised by CYP1A2. Pharmacokinetics may be affected by co-administration of other substances using this isoenzyme e.g. carbamazepine, fluvoxamine, nicotine.

Administration

- Orodispersible tablets can be dissolved in a drink immediately before oral administration.
- Orodispersible tablets can be dissolved in water for administration via feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy. Anecdotal reports that 5mg orodispersible tablets may be halved to give a 2.5mg dose: halve immediately before administration and discard the remaining portion.
- Coated tablets: swallow whole with liquid or crushed and mixed with soft food. Orodispersible tablets contain aspartame and may be harmful for people with PKU.

Patient information

- Patient information see Medicines for Children leaflet “Olanzapine for schizophrenia bipolar disorder mania and agitation https://www.medicinesforchildren.org.uk/medicines/olanzapine-for-schizophrenia-bipolar-disorder-mania-and-agitation/

Available as

- Tablets 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg; orodispersible tablets / lyophilisate, 5mg, 10mg, 15mg, 20mg.

Evidence: (1,2,87,266,267)

Omeprazole

Use:

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

Dose and route:

By mouth:

- **Neonate**: 700micrograms/kg once daily; increase if necessary to a maximum of 1.4mg/kg-2.8mg/kg once daily
- **Child 1 month-1 year**: 700micrograms/kg once daily; increase if necessary to a maximum of 3mg/kg or 20mg once daily
- **Child 10-19 kg**: 10mg once daily, increase if necessary to a maximum of 20mg once daily
- **20 kg and above**: 20mg once daily, increase if necessary to a maximum of 40mg once daily.

By intravenous infusion (over 20-30 minutes)

- **Child 1 month-11 years**: initially 500micrograms/kg, maximum 20mg/dose, once daily. Increase if necessary, to 2mg/kg, maximum 40mg/dose, once daily.
- **12 years and over**: 40mg once daily.

Notes:

- Proton pump inhibitor

Licensing

- Oral formulations are not licensed for use in children except for severe ulcerating reflux oesophagitis in children > 1 year. Infusion not licensed for use in children under 12years.

Therapeutics

- Many children with life limiting conditions have gastro-oesophageal reflux disease and may need to continue with treatment long term.

Side effects

- May cause agitation. Occasionally associated with electrolyte disturbance.
- MHRA safety warning 2015: very low risk of subacute cutaneous lupus erythematosus associated with use of PPIs.
- Constipation, diarrhoea, vomiting

Interactions

- Inhibits cytochrome P450 enzyme CYP2C19. May increase levels of drugs metabolised by this enzyme including diazepam.
- Metabolised by CYP2C19 and CYP3A4. Levels may increased by drugs that inhibit these enzymes including fluconazole.

Administration

- For oral administration tablets can be dispersed in water or mixed with fruit juice or yoghurt. Capsules can be opened and mixed with fruit juice or yoghurt.
- Administer with care via enteral feeding tubes to minimise risk of blockage. Capsules may be opened and contents dispersed in 8.4% sodium bicarbonate for administration. Dispersible tablets disintegrate to give a dispersion of small granules. The granules settle quickly and may block fine-bore feeding tubes (less than 8Fr). For administration via small bore tubes use of an oral suspension (unlicensed) is recommended. Omeprazole is absorbed when administered into the jejunum with no reduction in bioavailability. Choice of formulation depends on the size of tube.
- Intermittent subcutaneous administration has been reported at doses equivalent to the intravenous route, diluted to a concentration of 400micrograms/ml in sodium chloride 0.9%

Patient information

- Patient information see Medicines for Children leaflet “Omeprazole for gastro-oesophageal reflux disease (GORD)” https://www.medicinesforchildren.org.uk/medicines/omeprazole-for-gastro-oesophageal-reflux-disease-gord/

Available as

- Gastroresistant tablets (MUPS) tablets (10mg, 20mg, 40mg), capsules (10mg, 20mg, 40mg), intravenous infusion (40mg). Oral suspensions of strengths 10mg/5ml and 20mg/5ml are now available as licensed products in the UK. Other formulations of unlicensed oral suspensions are currently still available from UK ‘specials’ manufacturers.

Evidence: (1–3,8,130,131,268)

Ondansetron

Use:

- Antiemetic, particularly in vomiting caused by damage to gastrointestinal mucosa (e.g. chemotherapy or radiotherapy, severe gastroenteritis)
- Adjunct to levomepromazine in severe nausea and vomiting
- Opioid induced pruritus

Dose and route:

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

By intravenous infusion over at least 15 minutes

- **Child 6 months and over**: 5mg/m^2 or 150micrograms/kg immediately before chemotherapy maximum 8mg/dose.

  Dose can be repeated every 4 hours for 2 further doses before changing to oral route. Alternatively change to oral route after initial intravenous dose. Maximum total daily dose 32mg by any route

By mouth following intravenous administration

Oral dosing can start 12 hours after intravenous administration

- **Child 6 months and over:**

  Surface area less than 0.6m^2 or less than 10kg: 2mg every 12 hours for up to 5 days, maximum total daily dose 32mg

  Surface area 0.6m^2-1.2m^2 or 10- 40kg: 4mg every 12 hours for up to 5 days, maximum total daily dose 32mg

  Surface area over 1.2m^2 or over 40kg: 8mg every 12 hours for up to 5 days, maximum total daily dose 32mg

Nausea and vomiting, pruritus

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

- **Child 6 months and over**: 100-150micrograms/kg/dose every 8 -12 hours, maximum 8mg/dose

Notes:

- Serotonin ($5HT_3$) receptor antagonist

Licensing

- Injection licensed for the management of chemotherapy-induced nausea and vomiting in children over 6 months, and for the prevention and treatment of post-operative nausea and vomiting in children (as a single dose) from 1 month. Oral ondansetron licensed from 6 months of age for the management of chemotherapy-induced nausea and vomiting. Oral formulation not

recommended for post-operative nausea and vomiting in children due to a lack of data. Injection is not licensed for subcutaneous administration.

Therapeutics

- Pure $5HT_3$ antagonist, so receptor profile is complementary to levomepromazine. Consider for nausea and vomiting not controlled by regular levomepromazine.

Contraindications, cautions

- Contraindicated in patients with congenital long QT syndrome
- Prolongs QT-interval and associated with known risk of Torsades de Pointes even when taken as recommended. Caution in patients with cardiac disease and those with, or at risk of, prolonged QT-interval e.g. those with cardiac abnormalities, hypothyroidism, electrolyte imbalance or taking other drugs known to prolong the QT-interval

Side effects

- Powerfully constipating. Headache is a common adverse effect
- Possible side effects include nausea, vomiting, sweating and intestinal colic

Pharmacokinetics

- Decreased clearance in neonates (75%) in neonates and infants (50% at 3 months). Monitor closely if administered to children under 6 months. Consider increasing dosing interval and reducing dose.
- Onset of action oral less than 30 minutes, intravenous less than 5 minutes and duration 12 hours

Administration

- Orodispersible films should be placed on the tongue and allowed to disperse before swallowing. NB absorption of active drug does NOT occur via the oral mucosa, it is dependent on the dispersed tablet being swallowed
- For intravenous infusion, dilute to a concentration of 320–640micrograms/ml with dextrose 5% or sodium chloride 0.9% or Ringer's solution; give over at least 15 minutes.
- Oral solution contains sorbitol.
- Oral solution may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Case reports of administration by continuous subcutaneous infusion, diluted in sodium chloride 0.9% at concentrations of between 100micrograms/ml and 2mg/ml. Ondansetron injection has a low (acidic) pH and the formulation may cause localised site reactions particularly at higher concentrations.

Available as

- Tablets (4mg, 8mg, orodispersible films/tablets (4mg, 8mg), oral solution (4mg/5ml, 8mg/5ml), injection (2mg/ml, 2ml and 4ml amps).

Evidence: (1,2,11,32,269–273)

Oxybutynin

Use:

- Neurogenic or overactive bladder
- Symptomatic treatment of urinary incontinence, urgency and frequency in the unstable bladder whether due to neurogenic bladder disorders or idiopathic detrusor instability

Dose and route:

By mouth

Using immediate release preparation

- **Child up to 2 years**: 100-200micrograms/kg/dose 2-3 times daily. Maximum 12.5mg/dose
- **2-4 years**: 1.25-2.5mg/dose 2-3 times daily
- **5-11 years**: initial dose 2.5-3mg/dose twice daily, increasing to 5mg 2-3 times daily if needed
- **12 years and over**: initial dose 5mg/dose 2-3 times daily, increasing up to 5mg 4 times daily if needed

Using modified-release preparation

- **Child 5 years and over**: 5mg once daily adjusted, according to response, in increments of 5mg every week to a maximum of 15mg daily

Transdermal

Using Kentera® matrix patch

Approximate equivalent doses (see also notes below)

Oral oxybutynin 2.5–5mg/24hours	≡	¼ patch (1.3mg/24hours) twice weekly
Oral oxybutynin 5-10mg/24hours	≡	½ patch (2.6mg/24hours) twice weekly
Oral oxybutynin 10-15mg/24hours	≡	1 patch (3.9mg/24hours) twice weekly

Intravesical

- **Child 2 years and over**: 5mg 2-3 times daily

Notes:

- Antispasmodic with direct effect on smooth muscle and also inhibits the action of acetylcholine on smooth muscle. Increases bladder capacity, decreases uninhibited contractions and delays desire to void therefore decreasing urgency and frequency

Licensing

- Oral oxybutynin is not licensed for use in children less than 5 years of age. Intravesical and transdermal routes are not licensed in children. Intravesical formulation is unlicensed. Cutting patches is outside product licence

Therapeutics

- Transdermal administration of oxybutynin substantially bypasses the extensive first-pass metabolism that occurs with oral administration, reducing the formation of N-desethyloxybutynin (reducing systemic exposure to the active metabolites with a suggested reduction in incidence of adverse effects)
- An exact pharmacodynamic comparison between immediate release oxybutynin and transdermal oxybutynin is not possible due to their metabolic profiles being very different. There is no study of the therapeutic equivalence of immediate release oxybutynin and transdermal oxybutynin. The suggested starting point in dosing is derived from past efficacy response and is not exact because disease syndrome, patient response and acceptability is very diverse and unpredictable. Individual patient titration upwards or downwards is warranted to obtain the best therapeutic response.

Contraindications, cautions

- Contraindicated in myasthenia gravis, glaucoma, gastrointestinal obstructive disorders including paralytic ileus or intestinal atony, toxic megacolon, severe ulcerative colitis, bladder outflow obstruction
- Young children may be more sensitive to the adverse effects of oxybutynin, particularly the CNS and psychiatric adverse reactions.

Adverse Effects

- Common adverse effects due to antimuscarinic properties include: confusion, constipation, dizziness, drowsiness, dry mouth, dyspepsia, flushing, headache, nausea and vomiting, palpitations, tachycardia, blurred vision. Oral solutions containing sorbitol may cause diarrhoea

Renal Impairment and hepatic impairment

- Use with caution due to limited experience. Possible increased risk of adverse effects

Pharmacokinetics

- Transdermal: following application of the patch, oxybutynin plasma concentration increases for ~24-48 hours; steady state concentrations are reached during application of the second patch. Thereafter, steady concentrations are maintained for up to 96 hours

Interactions

- Increased risk of anticholinergic side effects with concurrent use of other anticholinergics
- By reducing gastric motility, oxybutynin may affect the absorption of other drugs and antagonise the effect of prokinetic medication

Administration

- Tablets should be swallowed whole to avoid unpleasant taste
- Apply patches should be applied to dry, intact skin on the abdomen, hip or buttock immediately after removal from the protective sachet. A new application site should be used with each new patch (do not reapply to same site within 7 days).
- Patches can be cut without affecting the mechanism, rate or amount of oxybutynin released. Transdermal patch may contain metal-remove patch prior to MRI
- Intravesical-after emptying the bladder, administer intravesical solution directly into the bladder via a catheter
- Use liquid formulation for administration via a feeding tube. Alternatively immediate release tablets may be crushed immediately prior to administration. Oxybutynin immediate release tablets may be crushed and mixed with water for administration via an enteral feeding tube. Flush well after administration. No specific data for jejunal administration: suggest administration as for gastrostomy, using liquid preparation, and monitor for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children Leaflet “Oxybutynin for daytime urinary symptoms” https://www.medicinesforchildren.org.uk/medicines/oxybutynin-for-daytime-urinary-symptoms/

Available as

- Immediate release tablets: 2.5mg, 3mg, 5mg. Modified-release tablets: 5mg, 10mg. Oral solution: 2.5mg in 5ml, 5mg in 5ml. Intravesical solution is available as an unlicensed special. Transdermal patches: patches contain 36mg of oxybutynin and release 3.9mg oxybutynin per 24 hours (Kentera®)

Evidence: (1–3,8,274–284)

Oxycodone

Use:

- Alternative opioid analgesic for severe pain

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in patients already receiving regular strong opioids

Convert using oral morphine equivalent (OME) from previous opioid analgesia, if applicable, see Appendix 1

By mouth using immediate release preparations

Conversion		Ratio	Calculation	Example
From	To			
Morphine oral	Oxycodone oral	2:1	Divide morphine oral dose by 2	Morphine oral 20mg ÷ 2 = oxycodone oral 10mg

Consider reducing the dose of oxycodone by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation

By mouth using modified release preparations

- Use oral morphine equivalent (as above) to convert current doses of previous opioid analgesia, if applicable, *then*
- Calculate the total daily dose (regular + PRN) of oral oxycodone administered over the previous 24 hours once the patient is established on regular strong opioid analgesia for 2-3 days

  12 hourly preparations: Divide the total daily dose of oral oxycodone by two and administer every 12 hours

  24 hourly preparations: Administer the total daily dose of oral oxycodone every 24 hours

  Ensure continued access to immediate release oxycodone as required for breakthrough pain see below

By single intravenous or subcutaneous bolus injection

Conversion		**Ratio**	**Calculation**	**Example**
From	**To**			
Oxycodone oral single dose	Oxycodone SC or IV bolus single dose	1.5:1	Divide oxycodone oral dose by 1.5	Oxycodone oral 4.5mg ÷ 1.5 = Oxycodone IV/SC *bolus* 3mg

Consider reducing the dose of oxycodone by ¼-½ when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

By continuous intravenous or subcutaneous infusion

Conversion		**Ratio**	**Calculation**	**Example**
From	**To**			
Morphine oral	Oxycodone CSCI or CIVI	3:1	Divide 24hour morphine dose by 3	Morphine oral 60mg/24hour ÷ 3 = oxycodone CSCI 20mg/24hours
Oxycodone oral	Oxycodone CSCI or CIVI	1:5:1	Divide 24hour dose of oral oxycodone by 1.5	Oxycodone oral 90mg/24hours ÷1.5 = oxycodone CSCI 60mg/24hours
Morphine CSCI or CIVI	Oxycodone CSCI or CIVI	1:1	Use the same dose	Morphine CSCI 50mg/24h = oxycodone CSCI 50mg/24hours

Consider reducing the dose of oxycodone by ¼-½ when the patient is already on a high dose of the previous opioid, when rotating due to intolerable side effects or when there has been a recent rapid escalation of the previous opioid

Breakthrough pain in patients already receiving opioids

By mouth using immediate release preparations, or by intermittent intravenous or subcutaneous bolus

- 1/10-1/6 of total daily oxycodone dose every 4-6 hours as required.

  Breakthrough and background (modified release, intravenous or subcutaneous infusion) doses should be reviewed if more than two breakthrough doses are required in a 24-hour period

Pain in opioid naïve patients

Opioid naive patients: the maximum dose stated applies to starting dose only

By mouth using immediate release preparations:

- **Child 1 month-11 years**[a]: Initial dose 100micrograms/kg, maximum single dose 5mg, every 4 -6 hours, increase as necessary according to severity of pain.
- **12 years and over**: Initial dose 5mg every 4-6 hours, increase as necessary according to severity of pain.

Notes:

- Opioid analgesic with similar efficacy and side effects to morphine. Generally, only appropriate for patients intolerant of morphine.

Licensing

- Not licensed for use in children less than 12 years of age. Available in combination with naloxone as alternative to laxative therapy in opioid-induced constipation Targinact® (Napp) not licensed in children.

Therapeutics

- Like morphine, oxycodone is primarily a Mu opioid receptor agonist. However, differences in structure mean that it may be effective for opioid substitution
- No neonatal dose available
- Reason behind odd conversion ratio is bioavailability and rounding factors for safety
- Strong oral solution has been used sublingually in adults
- Injection solution has been administered in children via sublingual and buccal routes. Doses equivalent to those given by mouth appear to be effective with similar onset of action and bioavailability: it is unclear how much of the drug is being absorbed via the transmucosal route and how much is being swallowed.
- Modified release preparations have also been administered via the rectal route
- Oral bioavailability may be lower in younger children and infants
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Cautions

- Caution in hepatic or renal impairment.

[a] Dose modified from BNFc taking into account APPM recommendations for morphine and equianalgesia

Side effects

- Usual opioid side effects

Interactions

- Metabolised by cytochrome P450 enzymes CYP2D6 and CYP3A4. Levels increased by drugs that inhibit these enzymes including celecoxib, ciprofloxacin, erythromycin and fluconazole. Levels reduced by drugs that induce these enzymes including carbamazepine and phenobarbital.

Administration

- Oxycodone injection may be given IV or SC as a bolus or by infusion. For CSCI, dilute with water for injection, 0.9% sodium chloride or 5% dextrose.
- Oxycodone liquid may be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administration as for gastrostomy and monitor for increased side effects or loss of efficacy.
- Modified release tablets are available as 12-hourly and 24-hourly preparations. Care with prescribing and do not confuse brands.

Available as

- Capsules (5mg, 10mg, 20mg), tablets (5mg),
- Oral solution (5mg/5 ml, 10mg/ml)
- Modified release tablets ***12-hourly*** (5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg, 120mg),
- Modified-release tablets ***24-hourly*** (10mg, 20mg, 40mg, 80mg)
- Injection (10mg/ml and 50mg/ml).

CD

- CD Schedule 2

Evidence: (1–3,8,62–64,71,72,113,285–287)

Oxygen

Use

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

Dose and route:

By inhalation through nasal cannula

- Flow rates of 1– 2.5L/min adjusted according to response.

  This will deliver between 24–35% oxygen depending on the patient's breathing pattern and other factors. Lower flow rates may be appropriate particularly for preterm neonates.

By inhalation through facemask

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

Notes:

Therapeutics

- No convincing evidence for O_2 in non-hypoxemic patients: moving air from a fan may be equally effective. Nevertheless, some patients do appear to benefit: try it and if it doesn't help stop.
- Oxygen has little effect in raising SaO_2 In cyanotic congenital heart disease and is not generally indicated. Pulmonary hypertension, in the early stages, may respond to oxygen.

Monitoring

- Oxygen saturations do not necessarily correlate with the severity of breathlessness. Observation of the work of breathing is a more reliable indicator of breathlessness where self-report is not possible.
- Decisions regarding target oxygen saturations and monitoring should be guided by the overall aims of oxygen treatment and realistic saturation levels for an individual child.
- Frequent or continuous measurement of oxygen saturations may lead to an over-reliance on technical data and distract from evaluation of the child's overall comfort, symptom relief and wellbeing.
- Usual target oxygen saturations of 92-96% are not necessarily appropriate for palliative care. More usual target oxygen saturations are above 92% in long-term oxygen therapy and 88-92% in children at risk of hypercapnic respiratory failure. Lower saturation levels may be tolerated in children with cyanotic congenital heart disease.

Side effects

- Continuous nasal oxygen can cause drying of the nasal mucosa and dermatitis.

Administration

- Nasal cannulae are generally preferable as they allow the child to talk and eat with minimum restrictions.
- Oxygen administration via a mask or via NIPPV can be claustrophobic and/or damage facial skin. This can be reduced by using a nasal mask. The duration of supply from an oxygen cylinder will depend on the size of the cylinder and the flow rate.
- An oxygen concentrator is recommended for patients requiring more than 8 hours oxygen therapy daily.
- If necessary, two concentrators can be Y-connected to supply very high oxygen concentrations.
- Liquid oxygen is more expensive but provides a longer duration of portable oxygen supply. Portable oxygen concentrators are now also available.
- Higher concentrations of oxygen are required during air travel.

Available as

- Currently Air Liquide (www.airliquidehealthcare.co.uk) and Dolby Vivisol (www.dolbyvivisol.com) provide home oxygen to the UK.

Evidence: (1–3,288–291)

Pamidronate (Disodium)

Use:

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

Dose and route:

Malignant hypercalcaemia

By intravenous infusion:

- **Child less than 2 years**: 500microgram/kg/dose
- **2- 3 years**: 750microgram/kg/dose
- **3 years and over**: 1mg/kg/dose, maximum 90mg/dose

Ensure adequate rehydration with intravenous sodium chloride 0.9%. Dilute pamidronate to a concentration of no more than 90mg/250ml sodium chloride 0.9% and infuse over 6 hours

Repeat up to weekly, as indicated by corrected serum calcium

Bone pain, metastatic bone disease, osteopenia, osteoporosis, osteogenesis imperfecta

By intravenous infusion:

Seek specialist advice

Age	Dose per infusion	Infusions per cycle	Repeat cycle	Alternative regimes
Child less than 2 years	500microgram/kg/dose	1 infusion daily for 3 consecutive days	Every 2 months	Can also be given as 750microgram/kg/infusion for 2 consecutive days every 2 months
Child 2- 3 years	750microgram/kg/dose	1 infusion daily for 3 consecutive days	Every 3 months	The same dose per infusion can also be given once every month OR the same dose per infusion can be given on 2 consecutive days every 2 months
Over 3 years	1mg/kg/dose maximum 60mg/dose	1 infusion daily for 3 consecutive days	Every 3 months	

Dilute pamidronate to a concentration of no more than 90mg/250ml 0.9% sodium chloride and infuse over 6 hours

Notes:

Licensing

- Not licensed for use in children. Not licensed for osteogenesis imperfecta.

Therapeutics

- Regimes vary between centres. Choice of regime depends on local guidelines and convenience. Some centres advise DEXA scan and investigations into calcium metabolism before and after treatment.
- Response to treatment of osteopenia or osteoporosis, and indications for on-going treatment, should be assessed after 1- 2 years treatment.
- Effectiveness of Pamidronate in bone pain does not necessarily depend on demonstrating osteoporosis, but demonstration that iatrogenic osteopetrosis has not developed afterwards can be reassuring.
- Pain may initially increase before improving.
- Improvement in bone pain may occur within two weeks in osteopenia or osteoporosis. However improvement in bone density may not be apparent for up to a year.
- Consider calcium and vitamin D oral supplements to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases and at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight).
- Other bisphosphonates are available in different formulations, including oral, although absorption tends to be poor by the oral route and further reduced by food or fluids other than plain water. Seek specialist advice.
- Denosumab is considered second line for refractory malignant hypercalcaemia

Caution

- Monitor renal function and electrolytes; ensure adequate hydration. Risk of renal impairment is increased by concurrent use with other nephrotoxic drugs

Interactions

- Prolonged hypocalcaemia and hypomagnesaemia may occur with concurrent use of aminoglycoside and a bisphosphonate.

Side effects

- Tolerated by children, but long term effects unknown.
- Flu-like symptoms are common with first infusion, but don’t necessarily recur with subsequent doses.
- Atypical femoral fractures, and of osteonecrosis especially of the jaw and the external auditory canal reported in adults. Risk in children is uncertain. Consider dental review before treatment, attention to dental hygiene together with patient and / or family education.

Administration

- Initial dose is usually given as an inpatient. Subsequent does could be given at home if necessary medical and nursing support is available.
- Can be administered by continuous subcutaneous infusion over 12-24 hours, together with subcutaneous hydration.

Available as

- Injection vials for infusion of various volumes, at 3mg/ml, 6mg/ml, 9mg/ml, 15mg/ml.

Evidence: (3,57,292–295)

Paracetamol

(US: Acetaminophen)

Use:

- Mild to moderate pain
- Pyrexia.

Dose and route:

Important safety information

MHRA advice: Paracetamol: updated dosing for children to be introduced (December 2014)

The recommended indications and doses of paracetamol have been revised to take account of MHRA and Toxbase advice that paracetamol toxicity may occur with doses between 75-150mg/kg/day.

APPM recommends body-weight-based dosing where possible because

- Many patients have lower than average body-weight for age
- Patients are more likely to be receiving paracetamol regularly
- Patients are more likely to be receiving enzyme inducing medication e.g. antiepileptics
- Patients are more likely to be at risk of hepatic and or renal impairment

By mouth:

Body-weight-based dosing: recommended

Warn parents or carers that doses may be different to "usual" doses stated on over the counter medication.

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

By rectum:

Body-weight-based dosing: recommended

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

By intravenous infusion over 15 minutes

- **Preterm neonate less than 32 week corrected gestational age**: 7.5mg/kg every 12 hours
- **Preterm neonate over 32 weeks corrected gestational age**: 7.5mg/kg every 8 hours
- **Neonate**: 10mg/kg every 4-6 hours, maximum 30mg/kg/day
- **Infant and child body-weight less than 10 kg**: 10mg/kg every 4-6 hours, maximum 30mg/kg/day
- **Child body-weight 10-50 kg**: 15mg/kg every 4-6 hours, maximum 60mg/kg/day
- **Body-weight over 50 kg**: 1g every 4-6 hours, maximum 4g/day

Notes:

Licensing

- Not licensed for use in children under 2 months by mouth; not licensed for use in preterm neonates by intravenous infusion; not licensed for use in children under 3 months by rectum; doses for severe symptoms not licensed; paracetamol oral suspension 500mg/5 ml not licensed for use in children under 16 years. IV infusion dose not licensed in children and neonates under 10kg.
- Oral and licensed rectal preparations are licensed for use in infants from 2 months for post immunisation pyrexia (single dose of 60mg which may be repeated once after 4-6 hours if necessary), and from 3 months as antipyretic and analgesic.
- Intravenous paracetamol is licensed for short term treatment of moderate pain, and of fever when other routes are not available.

Therapeutics

- Consider use of non-pharmacological measures to relieve pain, as alternative or in addition to analgesics.
- For management of feverish illness in children, see updated NICE clinical Guideline NG143. (Consider using either paracetamol or ibuprofen in children with fever who appear distressed and consider changing to the other agent if distress is not alleviated. Do not use antipyretic

agents with the sole aim of reducing body temperature). A recent Cochrane systematic review states “there is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone”.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

Contraindications, cautions

- Caution in duct dependent congenital heart disease. Administration may stimulate duct closure. Seek specialist cardiology advice.

Hepatic impairment, renal impairment

- Increase dosing interval to 6 hours in moderate renal impairment. Increase dosing interval to 8 hours in severe renal impairment.

Pharmacokinetics

- Onset of action 15-30 minutes by mouth. Onset of action 5-10 minutes IV for analgesia and 30 minutes IV as an antipyretic.
- May take up to 2 hours for full effects. Duration of action 4-6 hours orally and IV.
- Oral bioavailability 60-90%. Rectal bioavailability about 2/3 of oral. Rectal absorption is slower than oral, erratic and incomplete.
- Elimination is slower in babies under 3 months.

Side effects

- Hepatotoxic in overdose (more than 75mg/kg) or prolonged high doses.

Administration

- Oral preparation can be administered rectally and is absorbed more quickly than suppositories.
- Dispersible tablets have high sodium content (over 14mmol per tablet). Consider liquid preparation for regular administration
- For administration via an enteral feeding tube: Use tablets dispersed in water for intragastric or intrajejunal administration. If the sodium content is problematic, use the liquid formulation. This can be used undiluted for intragastric administration; however, the viscosity of the paediatric liquid preparations is very high; it is difficult to administer these suspensions via a fine bore tube without dilution. If administering intra-jejunally, dilute with at least an equal quantity of water to reduce osmolarity and viscosity.

Patient information

- See Medicines for Children leaflet “paracetamol for mild to moderate pain”: https://www.medicinesforchildren.org.uk/medicines/paracetamol/

Available as

- Tablets and caplets (500mg), capsules (500mg), soluble tablets (120mg, 500mg), oral suspension (120mg/5ml, 250mg/5ml), Fastabs 250mg, suppositories (60mg, 125mg, 250mg, 500mg and other strengths available from ‘specials’ manufacturers or specialist importing companies) and intravenous infusion (10mg/ml in 50ml and 100ml vials).

Evidence: (1,2,8,11,296–298)

Parecoxib

Use:

- Injectable NSAID
- Acute pain when the enteral route is unavailable
- Co-analgesic in cancer-related bone pain when the enteral route is unavailable

Dose and route:

By intravenous, deep intramuscular or subcutaneous bolus

- **Child 10-40kg**: 500microgram/kg/dose-1mg/kg/dose every 12 hours (maximum 40mg/dose)
- **40kg and over**: 20-40mg/dose every 12 hours

By continuous subcutaneous infusion

- **Child 10-40kg**: 1-2mg/kg/24hours (maximum 80mg/24hours)
- **40kg and over**: 40-80mg/24hours

Notes:

Pro-drug of the selective COX-2 inhibitor valdecoxib

Licensing

- Licensed in adults for short term management of post-operative pain. Not licensed in children

Therapeutics

- Celecoxib may be used as an enteral alternative

Contraindications, cautions

- May mask fever and other signs of inflammation
- Caution in cardiac, hepatic or renal impairment and those with asthma
- Contraindicated: active peptic ulceration, active GI bleeding or inflammatory bowel disease, and severe heart failure
- Contraindicated in hypersensitivity to parecoxib or other NSAIDs

Side effects

- All NSAIDs are associated with serious gastro-intestinal toxicity. Parecoxib is associated with low risk of gastro-intestinal toxicity. Consider prescription of a proton pump inhibitor with prolonged use.
- All NSAID use (including cyclo-oxygenase-2 selective inhibitors) can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of the baseline cardiovascular risk factors or duration of NSAID use. The greatest risk may be in those receiving high doses long term. Risks have not been quantified in children.

Hepatic and renal impairment

- Reduce dose by 50% or avoid in severe renal impairment, reduce dose by 50% in moderate liver impairment, avoid in severe liver impairment

Pharmacokinetics

- Onset of action 10–15min (IV/IM), duration of action 6–12hours

Interactions

- Moderate inhibitor of cytochrome P450 enzymes CYP2C19 and CYP2D6. May increase levels drugs metabolised by these enzymes including amitriptyline, fluoxetine, haloperidol, hydromorphone, levomepromazine, omeprazole, oxycodone, risperidone, tapentadol and tramadol.
- Metabolised by CYP3A4 and CYP2C9. Levels may be increased by drugs that inhibit these enzymes including erythromycin and sodium valproate. Levels may be reduced by drugs which induce this enzyme including carbamazepine, phenobarbital and phenytoin.

Administration

- Intravenous, subcutaneous or intramuscular injection: reconstitute 40mg vial with 2ml 0.9% Sodium chloride or 5% dextrose to give solution for injection of concentration 20mg/ml. IV bolus injection is given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle
- For continuous subcutaneous infusion dilute with sodium chloride 0.9% to maximal volume in a 30ml syringe. Do not mix with other drugs in a syringe driver

Available as

- 40mg vial powder for solution for injection

Evidence: (2,3,299–307)

Paraldehyde (rectal)

Use:

- Treatment of prolonged seizures and status epilepticus.

Dose and route:

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

- **Neonate**: 0.8ml/kg as a single dose.
- **1 month and over**: 0.8ml/kg, maximum 20ml as a single dose.

Notes:

Licensing

- Paraldehyde enema for rectal use is an unlicensed formulation and route of administration.

Contraindications, cautions

- Contra-indicated in gastric disorders and in colitis.

Side effects

- Rectal administration may cause skin irritation.

Pharmacokinetics

- Mean half-life 7.5 hours

Patient information

- See Medicines for Children leaflet “Paraldehyde (rectal) for stopping seizures” https://www.medicinesforchildren.org.uk/medicines/rectal-paraldehyde-for-stopping-seizures/

Available as

- Paraldehyde enema: premixed solution of paraldehyde in olive oil in equal volumes from ‘special-order’ manufacturers or specialist importing companies.

Evidence:(1,2,122,308–310)

Phenobarbital

Use:

- Epilepsy including status epilepticus
- Neonatal convulsive status epilepticus: step 3 (after 2nd benzodiazepine) in APLS protocol
- Commonly used first line for seizures in neonates
- Palliation of intractable seizures in end-of-life care
- Adjuvant in cerebral irritability
- Sedation
- Agitation refractory to midazolam in end-of-life care

Dose and route:

Status epilepticus, seizures or agitation in end-of-life care

By mouth, intramuscular bolus, slow intravenous injection or subcutaneous infusion

Loading dose

- Used to reach steady state quickly and avoid late toxicity due to accumulation. Phenobarbital doses will take between 5 and 30 days to achieve steady state unless a loading dose is given.
- **All ages**: 20mg/kg/dose, maximum 1g, by mouth, intramuscular bolus, slow intravenous injection or subcutaneous infusion over at least 20 minutes (but see notes below)
- In view of concerns regarding respiratory depression in patients actively dying some centres administer an initial half-loading dose of 10mg/kg followed by a further loading dose, if required, after 1-2 hours.

On-going treatment

- **Neonate**: 2.5-5mg/kg once or twice daily as maintenance.
- **Child 1month-11 years**: 2.5-5mg/kg, maximum 300mg/dose, once or twice daily. Total daily dose can also be given as a continuous infusion/24hours.
- **Child 12 years and over**: 300mg twice daily. Total daily dose can also be given as a continuous infusion/24hours.

Epilepsy, cerebral irritability

By mouth:

- **Neonate**: 2.5-5mg/kg once or twice daily
- **Child 1 month-11 years**: 1–1.5mg/kg twice daily, increased gradually as required, usual maintenance dose 2.5-4mg/kg once or twice daily
- **12 years and over:** 60–180mg once daily

Notes:

Licensing

- Licensed for seizures. Not licensed for agitation in end-of-life care.

Therapeutics

- Consider vitamin D supplementation in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium.
- For patients already on oral phenobarbital but needing parenteral treatment, doses equivalent to the patient's usual total daily dose of oral phenobarbital can be used.

Monitoring

- Monitoring therapeutic levels may not be appropriate depending on the indication for administration and because tolerance occurs.

Side effects

- Sedation, paradoxical agitation, confusion, respiratory depression, movement disorders
- Associated with osteopenia and increased risk of fractures.

Pharmacokinetics

- Elimination half-life of 2-6 days in adults, 1-3 days in children.

Interactions

- Induces cytochrome P450 enzyme CYP3A4. Reduces levels of numerous drugs including alfentanil, buprenorphine, carbamazepine, dexamethasone, fentanyl, ketamine, midazolam and paracetamol. *This list is not exhaustive –seek advice.*

Administration

- Tablets may be crushed for administration if preferred. The liquid preparations may be administered via an enteral feeding tube. For administration via a jejunostomy tube, dilution with water is recommended to reduce the liquid viscosity.
- Use a separate site to commence subcutaneous infusion. SC bolus injections should be avoided because they can cause tissue necrosis due to the high pH. Dilute injection solution 1 in 10 with water for injections (i.e. to maximum concentration of 20mg/ml) before intravenous or subcutaneous administration. Administer intravenously at not more than 1mg/kg/minute.

Patient information

- See Medicines for Children leaflet “Phenobarbital for preventing seizures”. https://www.medicinesforchildren.org.uk/medicines/phenobarbital-for-preventing-seizures/

Available as

- Tablets (15mg, 30mg, 60mg), oral elixir (15mg/5ml) and injection (15mg/ml, 30mg/ml, 60mg/ml and 200mg/ml). The licensed oral elixir of 15mg/5 ml contains alcohol 38% and it is preferable to obtain an alcohol free oral liquid (usually 50mg/5ml) via one of the specials manufacturers.

CD

- Schedule 3 CD (CD No Register Phenobarbital).

Evidence: (1–3,11,122,192,193,311)

Phenytoin

Use:

- Epilepsy: status epilepticus, tonic-clonic seizures, focal seizures and neonatal seizures
- Neuropathic pain

Dose and route:

Epilepsy, neuropathic pain

By mouth or short intravenous infusion

- **Neonate**: Initial intravenous loading dose 18mg/kg then 2.5-5mg/kg twice daily by mouth adjusted according to response and plasma phenytoin levels. Usual maximum 7.5mg/kg twice daily.
- **1 month-11 years**: 1.5-2.5mg/kg twice daily adjusted according to response and plasma phenytoin levels. Usual target maintenance dose to 2.5-5mg/kg twice daily. Usual maximum dose of 7.5mg/kg twice daily or 300mg daily.
- **12 years and over**: 75-150mg twice daily adjusted according to response and plasma phenytoin levels. Usual target maintenance dose 150-200mg twice daily. Usual maximum dose of 300mg twice daily.

Status epilepticus

By short intravenous infusion

- **Neonate**: Loading dose 20mg/kg, then 2.5-5mg/kg/dose twice daily adjusted according to response and plasma phenytoin levels.
- **1 month-11 years**: Loading dose 20mg/kg, then 2.5-5mg/kg twice daily adjusted according to response and plasma phenytoin levels.
- **12 years and over**: Loading dose 20mg/kg, maximum 1g, then 150mg twice daily adjusted according to response and plasma, phenytoin levels

Notes:

- Membrane stabiliser.

Licensing

- Suspension 90mg in 5ml is a ‘special’ and unlicensed. Other preparations are licensed for use in children as an anticonvulsant.

Therapeutics

- Third or fourth line for epilepsy and for neuropathic pain
- Oral doses are usually as effective as intravenous above 2 weeks old. Older babies may need higher doses.
- Cross-sensitivity is reported with carbamazepine.

- Avoid abrupt withdrawal.
- Consider vitamin D supplementation in patients at risk of osteopenia or vitamin D deficiency.
- Prescribe oral preparations by brand name: bioavailability may vary with brand.
- Use adjusted body weight (Appendix 7) to calculate doses in obese children

Side effects

- Associated with osteopenia and increased risk of fractures. Consider vitamin D supplementation with long term use.
- Arrythmias, hypotension and respiratory depression with parenteral use

Pharmacokinetics

- Narrow therapeutic index, unpredictable half-life, and non-linear relationship between dose and plasma-drug concentration. Marked variation in rate of elimination, especially in the first few weeks and months of life.
- Oral bioavailability 90-95% is roughly equivalent to intravenous, plasma half-life 7-42 hours. Poor rectal absorption.

Interactions

- Induces cytochrome P450 enzymes CYP1A2 and CYP3A4. Reduces levels of numerous drugs including alfentanil, buprenorphine, carbamazepine (also increasing levels of phenytoin), dexamethasone, diazepam, fentanyl, ketamine, melatonin midazolam and paracetamol. *This list is not exhaustive –seek advice.*
- Long term use is associated with significant side effects. No more effective than other anti-epileptics but doses can be titrated quickly.

Hepatic impairment, renal impairment

- Reduce dose in hepatic impairment. Monitor carefully if reduced albumin or protein binding e.g. in renal failure.

Administration

- Administer infusions over at least 20 minutes and at a rate not exceeding 1mg/kg/minute, maximum 50mg/minute. Monitor ECG and blood pressure during administration.
- Dilute to a concentration not exceeding 10mg/ml with Sodium Chloride 0.9% for intravenous infusion. Administer into a large vein through an in-line filter (0.22–0.50 microns); complete administration within 1 hour of preparation. Flush intravenous line with Sodium Chloride 0.9%. before and after administration,
- Preparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base (such as Epanutin Infatabs® and Epanutin® suspension); 100mg of phenytoin sodium is approximately equivalent in therapeutic effect to 92mg phenytoin base. The dose is the same for all phenytoin products when initiating therapy, however if switching between these products the difference in phenytoin content may be clinically significant. Care is needed when making changes between formulations and plasma phenytoin concentration monitoring is recommended.
- Bioavailability may be reduced unpredictably by enteral feeds and/or nasogastric tube feeds, so flush with water to enhance absorption, interrupt enteral feeding for at least 1-2 hours before and after giving phenytoin, and maintain similar timings and regimes from day to day. Use the oral suspension for enteral tube administration; dilution with an equal volume of water is recommended for gastrostomy administration. Absorption is exceptionally poor via the jejunal route; plasma concentration should be monitored closely if this route is used. Dilution of the suspension is important as phenytoin suspension is hyperosmolar and may cause diarrhoea when administered into the jejunum.

Patient information

- See Medicines for Children leaflet “Phenytoin for preventing seizures”. https://www.medicinesforchildren.org.uk/medicines/phenytoin-for-preventing-seizures/

Available as

- Tablets (phenytoin sodium 100mg, generic), capsules (phenytoin sodium 25mg, 50mg,100mg, 300mg), Epanutin® Infatabs (chewable tablets of phenytoin base 50mg), oral suspension (Epanutin® phenytoin base 30mg/5ml, and 90mg/5ml phenytoin base available as an ‘unlicensed special’), and injection (phenytoin sodium 50mg/ml generic)

Evidence: (1–3,8,122,311)

Phosphate (rectal enema)

Use:

- Constipation refractive to other treatments.

Dose and route:

By rectum:

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

- **Child 3-6 years**: 45-65ml once daily.
- **Child 7-11 years**: 65-100ml once daily.
- **12 years and over**: 100-128ml once daily.

Cleen® (previously Fleet®) Ready to Use enema:

- **Child 3-6 years**: 40-60ml once daily.
- **Child 7-11 years**: 60-90ml once daily.
- **12 years and over**: 90-118ml once daily.

Notes:

Therapeutics

- Onset of action 2-5 minutes

Contraindications, cautions

- Contraindicated in acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption).
- Use only in faecal impaction if all oral medications, and rectal sodium citrate have failed.

Side effects

- Risk of dehydration and electrolyte disturbance.
- Case reports of hyperphosphataemia and tetany following use of phosphate enemas in children. Risk is likely to be increased with use more than once or twice per week or higher doses.

Administration

- May be warmed to body temperature in a water bath prior to administration

Available as

- Phosphate enema BP Formula B (with standard or long rectal tube), Cleen® Ready to Use enema

Evidence: (1–3,312,313)

Pregabalin

Use:

- Epilepsy (focal seizures with or without secondary generalisation)
- Peripheral and central neuropathic pain
- Generalised anxiety disorder
- Restless legs syndrome in chronic kidney disease
- Pruritus associated with burns

Important safety information

MHRA/CHM advice: Pregabalin (Lyrica®): reports of severe respiratory depression (February 2021)

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

Dose and route:

Neuropathic pain and pruritus, adjunctive therapy for focal seizures, anxiety, restless legs

By mouth:

- **Child 1 month- 15 years:** 1mg/kg/dose twice daily

  Increase every 3-7 days by 500micrograms/kg/dose until desired therapeutic effect or side effects experienced.

  Initial maximum 5mg/kg twice daily

  Younger children under 30kg and especially those under 6 years may require up to 15mg/kg/day. Maximum 300mg twice daily

- **Adult 16 years and over:** 75mg twice daily

  Increase every 3-7 days by 75mg/dose until desired therapeutic effect or side effects experienced.

  Maximum 300mg twice daily

Gabapentin to Pregabalin switch for neuropathic pain

See Appendix 5

Notes:

Licensing

- Licensed in adults as an adjunct for partial seizures; for the treatment of peripheral and central neuropathic pain and for the treatment of generalised anxiety disorder. Not licensed for use in children or adolescents less than 18 years of age.

Therapeutics

- Binds to the alpha-2 subunit of voltage gated calcium channels in the CNS thus inhibiting the release of excitatory neurotransmitters. Six times greater receptor affinity than gabapentin
- Younger children less than 6 years may need up to 15mg/kg/day particularly for seizures
- Do not stop abruptly: discontinue gradually over a minimum of one week

Hepatic impairment, renal impairment

- Excreted unchanged via kidneys, reduce dose in renal impairment. Recommended maximum doses in renal impairment:

Body-weight	Mild renal impairment Creatinine clearance 31-60ml/min	Moderate renal impairment Creatinine clearance 15-30ml/min	Severe renal impairment Creatinine clearance <15ml/min
Less than 30kg	7mg/kg/24hours	3.5mg/kg/24hours	1.4mg/kg/24hours
More than 30kg	5mg/kg/24hours	2.5mg/kg/24hours	1mg/kg/24hours

- No dose modification required in hepatic impairment

Pharmacokinetics

- Oral bioavailability 90% or greater. Peak plasma concentrations occur within 1.5 hours.
- Drug clearance is faster in children under 30 kg. Higher doses and/or more frequent dosing interval may therefore be needed in younger children, particularly those under 6 years of age

Side effects

- Most commonly reported adverse effects are dizziness, somnolence and headache. These are generally transient and mild to moderate in nature and may be minimised by a gradual increase to the therapeutic dose.
- Pregabalin may exacerbate seizures in patients with absence or myoclonic seizures (including juvenile myoclonic epilepsy), tonic or atonic seizures, Dravet syndrome, Lennox-Gastaut syndrome, and myoclonic-atonic seizures.

Administration

- Use the oral solution for administration via an enteral tube. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

Available as

- Oral capsules (25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg and oral solution (20mg/ml).
- Schedule 3 controlled drug although exempt from safe storage requirements.

Evidence: (2,3,159,161,162,314–322)

Promethazine hydrochloride

Use:

- Sleep disturbance.
- Mild sedation
- Symptomatic relief of allergy
- Nausea and vomiting (including motion and opioid-induced), and vertigo
- Sedation in neonatal intensive care

Dose and route:

Important safety information

MHRA/CHM advice: Over-the-counter cough and cold medicines for children (April 2009)

Children under 6 years should not be given over-the-counter cough and cold medicines containing promethazine.

Contraindications

Promethazine should not be given to children under 2 years, except on specialist advice, due to the potential for fatal respiratory depression

Symptomatic relief of allergy:

By mouth:

- **6- 23 months:** 2.5mg–5mg twice daily (on specialist advice)
- **Child 2- 4 years**: 5mg twice daily or 5-15mg at night.
- **Child 5- 9 years**: 5–10mg twice daily or 10–25mg at night.
- **10 years and over**: 10–20mg 2–3 times daily or 25mg at night increased to 25mg twice daily if necessary.

Sedation (short term use):

By mouth:

- **6- 23 months**: 5-10mg at night (on specialist advice)
- **Child 2- 4 years**: 15-20mg at night.
- **Child 5- 9 years**: 20-25mg at night.
- **10 years and over**: 25-50mg at night.

Nausea and vomiting (particularly in anticipation of motion sickness)

By mouth

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

Sedation in intensive care

By mouth, by slow intravenous injection or by deep intramuscular injection

- **Neonate greater than 37 weeks corrected gestational age**: 500microgram/kg –1mg/kg 4 times daily, adjusted according to response
- **Child 1 month-11 years:** 500microgram/kg-1mg/kg 4 times daily, maximum 25mg/dose, adjusted according to response
- **12 years and over:** 25-50mg/dose 4 times daily adjusted according to response

Notes:

- Antihistamine (anti H1) with moderate muscarinic and D2 receptor antagonism. Significant antimuscarinic activity, particularly in neonates

Licensing

- Not licensed for sedation in children under 2 years

Therapeutics

- Has also been used orally for dyspnoea in adults.
- Used in neonatal units on bigger babies for oral sedation when usual IV sedation options ineffective.
- Start at 25% oral doses if administered intravenously or subcutaneously outside intensive care environment.

Contraindications, cautions

- Caution in epilepsy, asthma. Risk of hypotension if co-prescribed with opioid.

Side effects

- Respiratory depression, arrythmias, movement disorders including neuroleptic malignant syndrome, urinary retention, insomnia, seizures, nausea and vomiting.

Pharmacokinetics

- Oral bioavailability approximately 25%.

Hepatic impairment, renal impairment

- Caution in renal and severe hepatic impairment

Interactions

- Risk of drug interactions with other antimuscarinic or sedative drugs.

Administration

- Not generally recommended for subcutaneous administration due to the risk of local necrosis, but diluted in an adequate volume of sodium chloride 0.9% can usually be administered by CSCI/24hours. Do not give bolus SC injections.
- Oral preparation can be effective for up to 12 hours. Peak plasma concentration 2-3 hours after administration. Drowsiness may wear off after a few days of treatment.
- Use oral preparation for administration via gastrostomy. Dilute oral preparation with an equal volume of water for jejunal administration. Tablets will disintegrate if shaken in water for 5 minutes.

Available as

- Promethazine hydrochloride tablets (10mg, 25mg), oral elixir (5mg/5 ml), and injection (25mg/ml). (Promethazine teoclate tablets also available, 25mg, licensed for nausea, vertigo and labyrinthine disorders. Slightly longer acting than promethazine hydrochloride and dosing slightly different).

Evidence: (1,3,8,11)

Propantheline bromide (NEW)

Use:

- Smooth muscle spasm (bladder and gastrointestinal tract)
- Anti-secretory
- Hyperhidrosis

Dose and route:

By mouth

Take at least one hour before food

- **1month-11 years**: 300micrograms/kg/dose, maximum 15mg, 3-4 times daily
- **12 years and over**:: 15mg three times daily *and* 30mg at night, maximum 120mg/day

Notes:

- Quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine

Licensing:

- Not licensed for use in children

Therapeutics

- Acts by two distinct mechanisms: non-specific acetylcholine antagonist at muscarinic M1–3 receptors, *and* a direct musculotropic effect causing relaxation of smooth muscle.
- Possible clinical benefits include decreased respiratory tract secretions, decreased gastric acid production, smooth muscle relaxation. Specific benefits for hyperhidrosis (excessive sweating) and gustatory sweating are attributed to its antagonism of acetylcholine at M3 receptors of glandular tissue.

Contraindications, cautions

- Contraindicated in gastro-intestinal obstruction and ileus, urinary retention, myasthenia gravis
- Caution in arrythmias, cardiac failure, pyrexia, ulcerative colitis, gastro-oesophageal reflux

Side effects

- Antimuscarinic side effects include dry mouth, drowsiness, headache, fatigue, dizziness, thickening of bronchial secretions, nervousness.

Administration

- Can be administered via gastrostomy. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

Available as

- Tablets 15mg, oral suspension and oral solution from special-order manufacturers.

Evidence: (1,323–329)

Prucalopride (NEW)

Use:

- Prokinetic agent for treatment of constipation when laxatives are ineffective / inadequate
- Second line prokinetic for upper gastrointestinal dysmotility

Dose and route:

By mouth

- **Child up to 12 years or less than 50kg**: 30-40micrograms/kg/dose, maximum single dose 2mg, once daily
- **12 years and over *and* 50kg or over**: 2mg once daily

Notes:

- Selective 5-HT4 receptor agonist with and enterokinetic effect increasing GI motility.

Licensing:

- Not licensed for use in children under 18 years of age.

Contraindications, cautions

- Contraindicated in Crohn's disease; intestinal obstruction; intestinal perforation; toxic megacolon; ulcerative colitis.
- Caution in history of arrhythmias

Hepatic impairment, renal impairment

- Reduce dose in severe renal and/or hepatic impairment.

Side effects:

- Headache, dizziness, fatigue and gastrointestinal symptoms (abdominal pain, decreased appetite, GI discomfort, nausea and diarrhoea). Adverse effects occur predominantly at the start of therapy and usually disappear within a few days within continued treatment.

Administration:

Tablets may be crushed and dispersed in water to aid administration (off-label) but may have an unpleasant taste. No information on administration via an enteral feeding tube.

Available as

- 1mg and 2mg tablets.

Evidence:(2,330–352)

Risperidone

Use:

- Severe neuro-irritability
- Dystonia and dystonic spasms refractory to first and second line treatment
- Delirium
- Short term treatment of persistent aggression in conduct disorder in children and in autism or moderate to severe dementia
- Psychosis in Battens disease
- Treatment of acute mania or psychosis (under specialist supervision)

Dose and routes

Severe neuro-irritability, refractory dystonia, delirium, aggression

By mouth:

- **Child 1 month-11 years, body-weight up to 50kg**: 10micrograms/kg once daily, maximum 500micrograms/dose, increasing if necessary to 20micrograms/kg once daily after 3-7 days

  Increase gradually if required, every 7-14 days in increments of 10micrograms/kg/day to a maximum of 60micrograms/kg/day, maximum 3mg/day

- **12 years and over, body-weight over 50kg:** 500micrograms once daily increasing if necessary to 1mg once daily after 3-7 days

  Increase gradually if required, in increments of 500micrograms every 7-14 days to a maximum of 3mg/day

Acute mania or psychosis (under specialist supervision), psychosis in Batten's disease

Higher doses, more rapid titration

By mouth:

- **Child 1 month-11 years, body-weight up to 50kg**: 10micrograms/kg, maximum 500micrograms/dose, twice daily; increased on day 2 to 20micrograms/kg, maximum 1mg/dose, twice daily and 30micrograms/kg, maximum 1.5mg/dose, twice daily from day 3

  Increase further if required, and as tolerated. Usual maximum 3mg twice daily

- **12 years and over, body-weight over 50kg:** 500micrograms twice daily, increased on day 2 to 1mg, twice daily and 1.5mg twice daily from day 3

  Increase further if required, and as tolerated. Usual maximum 3mg twice daily

Notes

- Dopamine D2, 5-HTA, alpha-1 adrenoceptor and histamine-1 receptor antagonist.

Licensing

- Not licensed for use in children for psychosis, mania, or autism..

Therapeutics

- Usual maintenance dose in adolescents and adults with psychosis or mania is 4-8mg/day.
- Children with Juvenile Battens Disease may need up to 1.5mg 3 times daily during crises with hallucinations: this dose can be reduced or stopped as symptoms settle (episodes usually last 1-6 weeks).
- Maximum adult dose 16mg/day however doses above 10mg/day have not been shown to be more effective and side effects are more likely.
- Some experience as an anti-emetic in refractory nausea and vomiting in adults; not evaluated in children
- Total daily dose can be given once at bedtime.

Contraindications, cautions

- Caution in epilepsy (lowers seizure threshold) and cardiovascular disease; extrapyramidal symptoms less frequent than with older antipsychotic medications; can cause orthostatic hypotension; withdraw gradually after prolonged use.

Side effects

- Weight gain. Other common side effects include anxiety, depression, sleep disorders, hypertension, oedema, malaise, constipation.
- Neuroleptic malignant syndrome

Hepatic impairment, renal impairment

- Initial and subsequent doses should be halved in renal or hepatic impairment.

Pharmacokinetics

- Oral bioavailability 99%. 1-2 hours to peak plasma concentration. Onset of action hours to days in delirium; days to weeks in psychosis. Plasma half-life 24 hours. Duration of action 12-48 hours.

Administration

- Oral liquid may be diluted in any non-alcoholic drink except tea. Orodispersible tablets should be placed on the tongue, allowed to dissolve and swallowed. Use oral liquid for administration via enteral feeding tubes. Tablets also disintegrate in water within 5 minutes for easy administration via enteral feeding tubes. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet “Risperidone for psychological disorders”. https://www.medicinesforchildren.org.uk/medicines/risperidone-for-psychological-disorders /

Available as

- Tablets (500micrograms, 1mg, 2mg, 3mg, 4mg, 6mg), orodispersible tablets (500micrograms, 1mg, 2mg, 3mg, 4mg), oral solution 1mg/ml.

Evidence: (2,3,8,87,353–362)

Salbutamol

Use:

- Breathlessness or wheeze caused by bronchospasm including exacerbations associated with respiratory tract infection.
- Prevention and treatment of chronic lung disease in premature infants
- Hyperkalaemia.

Dose and route:

Exacerbation of reversible airway obstruction, prevention of allergen-or exercise-induced bronchospasm

By aerosol inhalation:

Use via large volume spacer (and a close-fitting face mask in children under 3 years).

- **Child 1 month and over**: 100-200micrograms (1-2 puffs) up to four times daily.

By inhalation of nebulised solution:

- **Neonate:** 1-2.5mg up to four times daily
- **Child 1 month-4 years**: 2.5mg up to four times daily
- **5-11 years**: 2.5-5mg, up to four times daily.
- **12 years and over**: 5mg, up to four times daily

Emergency treatment of moderate to severe acute asthma

N.B. Use in this context typically given in hospital setting to enable escalation of treatment if required. See separate detailed guidance in standard texts for use in acute life-threatening asthma

By aerosol inhalation:

- **Child 1 month and over**: 200-1000micrograms (2–10 puffs), each puff is to be inhaled separately, repeat every 10–20 minutes or when required, give via large volume spacer (and a close-fitting face mask in children under 3 years).

By inhalation of nebulised solution (*inpatient settings only*)

- **Child 1 month-4 years**: 2.5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.
- **5-11 years**: 2.5-5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.
- **12 years and over**: 5mg, repeated every 20-30minutes, or when required and administered by oxygen-driven nebuliser if available.

Hyperkalaemia

See separate detailed guidance in standard texts

Notes

Short acting beta 2 adrenergic receptor agonist

Licensing

- Salbutamol is not licensed for use in hyperkalaemia; injection is not licensed for use in children.

Therapeutics

- Spirometry should normally be used to confirm a possible underlying asthma diagnosis.
- In palliative care, if airflow obstruction is suspected, a pragmatic approach may be to give a trial (e.g. 1–2 weeks) of a bronchodilator and evaluate the impact on symptoms.
- Clinical efficacy of salbutamol in infants <18 months is uncertain, presumably due to the immaturity of the receptors; ipratropium may be more helpful in those less than 1-2 years. No evidence of efficacy in infection-related bronchospasm in infants
- Oral liquid is generally used only in the context of slowing rate of degradation of motor neurone proteins in neuromuscular disease. Seek specialist advice
- In children over the age of 5 years with mild and moderate acute asthma attacks, a pressurised metered-dose inhaler with a spacer is at least as effective as nebulisation.
- Ipratropium bromide is an appropriate alternative if side effects prevent use
- Advise family to seek advice if a previously effective dose fails to provide at least 3 hours relief, and warn of the dangers of exceeding prescribed inhaler and nebuliser doses.

Contraindications, cautions

- Risk of tachycardia and risk of QT prolongation at increasing doses.

Side effects

- Increased heart rate; feeling “edgy” or agitated; tremor. Rarely paradoxical bronchospasm can occur in response to beta-2-adrenoceptor agonists, hypokalaemia

Pharmacokinetics

- Onset of action 5 minutes via inhalation of aerosol, 3-5 minutes nebulised. Peak response 0.5-2 hours. Duration of action 4-6 hours. Only 10-20% of inhaled dose reaches lower airways.

Interactions

- Increased risk of hypokalaemia with corticosteroids, diuretics, theophylline.

Administration

- Inhaled product should be used with a suitable spacer device. The carer, and child where appropriate, should be given appropriate training. Inhaler technique should be explained and checked. The HFA (hydrofluoroalkane) propellant now used in multi-dose inhalers tends to clog the nozzle, so weekly cleaning is recommended.
- Salbutamol 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% Sodium chloride. Salbutamol can be mixed with nebulised solution of ipratropium bromide.

Patient information

- See Medicines for Children leaflet “Salbutamol for asthma and wheeze”. https://www.medicinesforchildren.org.uk/medicines/salbutamol-inhaler-for-asthma-and-wheeze/

Available as

- Nebuliser solution (2.5mg/2.5ml, 5mg in 2.5 ml), respirator solution (5mg/ml), aerosol inhalation (100 micrograms/puff) by metered dose inhaler (MDI), with various spacer devices. Various types of dry powder inhaler are also available, 100 and 200 micrograms per puff., injection (500 micrograms/ml), intravenous infusion (1mg/ml) oral solution (2mg/5ml), tablets (2mg and 4mg).

Evidence: (1,2,11,363,364)

Senna

Use:

- Constipation (stimulant laxative)

Dose and route:

By mouth:

Start at low dose, increasing as necessary after 24–48 hours

- **Child 1 month-3 years:** 3.75-15mg once daily, adjusted according to response.
- **4-5 years:** 3.75-30mg once daily, adjusted according to response.
- **6-17 years:** 7.5-30mg once daily, adjusted according to response.

Notes:

- Stimulant laxative acting on large bowel.

Licensing

- Oral solution is not licensed for use in children < 2 years and tablets are not licensed for use in children <6 years

Therapeutics

- Improves intestinal motility and increases water secretion into bowel lumen. Senna passes unchanged into large bowel. Hydrolysed by bacterial flora in the large bowel to yield the active compound.
- NICE Guidance CG99: Constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives prior to a trial of a stimulant laxative. However, senna is considered the drug of first choice for opioid induced constipation in palliative care
- Optimise dose before adding a second agent
- Doses can be exceeded on specialist advice: opioid induced constipation often requires higher doses than in manufacturer's Product Information.
- Onset of action 8-12 hours.
- Available in the UK as an "over the counter" medicine for short courses in adults only

Contraindications, cautions

- Contraindicated in atony, intestinal obstruction, undiagnosed abdominal pain

Side effects

- Abdominal pain. Prolonged use or excessive use can cause hypokalaemia.

Administration

- Oral liquid may be administered via an enteral feeding tube; flush well before and after the dose. Therapeutic effect will be unaffected by jejunal administration.

Patient information

- See Medicines for Children leaflet “Senna for constipation”. https://www.medicinesforchildren.org.uk/medicines/senna-for-constipation/

Available as

- Tablets (7.5mg sennoside B) and oral suspension (7.5mg/5ml sennoside B)

Evidence: (1–3,8,313,365,366)

Sodium Citrate

Use:

- Constipation (osmotic laxative)

Dose and routes:

By rectum

Micolette Micro-enema

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

- **Child 3 years and over**: 5–10ml as a single dose

Micralax Micro-enema

Sodium citrate 450mg, sodium alkylsulfoacetate 45mg, sorbic acid 5mg, together with glycerol and sorbitol in a viscous solution in 5ml

- **Child 3 years and over**: 5ml as a single dose

Relaxit Micro-enema

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

- **Child 1 month and over:** 5ml as a single dose (insert only half nozzle length in child 2 years or under).

Notes

- Osmotic laxative

Licensing

- Licensed for treatment of constipation for all ages

Therapeutics

- Usually combined with faecal softener (e.g. sodium lauryl sulphate, sodium alkylsulfoacetate) in micro-enemas.
- Sodium citrate is an osmotic agent. Sodium lauryl sulfoacetate is a faecal softener.
- Used where oral laxatives are ineffective or not feasible. Micro-enema, often used in combination with oral laxatives, particularly in neuromuscular disorders, faecal loading and faecal impaction.
- NICE Guidance for the management of constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives and stimulant laxatives before the use of

rectal measures. Sodium Citrate is considered the first line rectal measure, in preference to phosphate enemas.
- Usually acts within 15 minutes of administration

Contraindications, cautions

- Contraindicated in acute gastro-intestinal conditions
- Caution: can cause harmful sodium and water retention in susceptible patients.

Side effects

- Abdominal discomfort

Available as

- Micro-enema (5ml). All currently marketed preparations include sodium citrate 90mg/ml, but other constituents vary.

Evidence: (1,2,313)

Sodium Picosulfate

Use:

- Constipation (stimulant laxative).

Dose and routes:

By mouth:

- **Child 1 month-3 years**

  Less than 10kg: 250micrograms/kg once daily

  More than 10kg: 2.5mg once daily

  Increase as necessary according to response to a suggested maximum of 10mg daily

- **Child 4 years and over**: Initial dose of 2.5mg once daily increase as necessary according to response to a suggested maximum of 20mg daily.

Notes

- Stimulant laxative

Licensing

- Oral suspension is licensed for use in children; capsules are not licensed for use in children less than 4 years of age.

Therapeutics

- NICE Guidance CG99: Constipation in children and young people advocates the use of polyethylene glycol 3350 containing laxatives prior to a trial of a stimulant laxative. However, for opioid induced constipation in palliative care, senna is a considered the first line choice. If ineffective at first, dose should be optimised and only add a second agent if not adequately effective.
- Effectiveness dependent upon breakdown by gut flora-previous effectiveness may therefore be lost during courses of antibiotics and ensuing altered gut flora.
- Onset of action 6-12 hours.

Contraindications, cautions

- Contraindicated in intestinal obstruction and undiagnosed abdominal pain

Side effects

- Prolonged use or excessive use can cause hypokalaemia.

Administration

- Use the liquid preparation for administration via an enteral feeding tube; dilute with an equal volume of water. Sodium picosulfate reaches the colon without any significant absorption; therefore, the therapeutic response will be unaffected by jejunal administration.

Patient information

- See Medicines for Children leaflet " sodium picosulfate for constipation" https://www.medicinesforchildren.org.uk/medicines/sodium-picosulfate-for-constipation/

Available as

- Oral solution (5mg/5ml) and capsules (as Dulcolax PicoPerles 2.5mg). Also available mixed with Magnesium citrate for bowel evacuation prior to procedures (Picolax and Citrafleet).

Evidence: (1,2,8,313)

Sucralfate

Use:

- Prophylaxis of stress ulcer.
- Prophylaxis of bleeding from oesophageal or gastric varices
- Adjunct in the treatment of: oesophagitis with evidence of mucosal ulceration, gastric or duodenal ulceration,
- Upper gastro intestinal tract bleeding of unknown cause.
- Haemostasis (topical use).

Dose and route:

Prophylaxis and adjunctive treatment of upper GI tract bleeding

By mouth

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

Topical haemostasis

- Sucralfate suspension (1g/5ml) can be applied to the affected area twice daily e.g. as mouth wash, orally for oesophageal lesions, rectally for rectal lesions.
- Sucralfate paste (2 x 1g tablets crushed in 5ml aqueous jelly lubricant, or water) applied to the affected area twice daily

Notes:

- Complex of aluminium hydroxide and sulphated sucrose.

Licensing

- Not licensed for use in children less than 15 years; tablets are not licensed for prophylaxis of stress ulceration.

Therapeutics

- In the gut it seems to act by protecting mucosa from acid-pepsin attack. Minimal antacid properties. Acts locally and is minimally absorbed.
- Spread doses evenly throughout waking hours.

Side effects

- Case reports of bezoar formation with sucralfate.

Contraindications, cautions

- Caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying.
- Caution: absorption of aluminium from sucralfate may be significant in patients on dialysis or with renal impairment.

Pharmacokinetics

- Onset of action 1-2 hours, duration of action 6 hours.

Administration

- Administration of sucralfate suspension and enteral feeds via a NG or gastrostomy tube should be separated by at least 1 hour to avoid formation of an insoluble complex that may block fine-bore feeding tubes. By mouth sucralfate should be given 1 hour before meals to reduce chance of bezoar formation. Suggest diluting with water before administration. Not appropriate for jejunal administration as the site of action is gastric and duodenal.
- Tablets may be crushed and dispersed in 10-15 ml water.

Available as

- Oral suspension (1g/5ml special order), tablets (1g). Oral suspension, cream, powder and enema available as special order.

Evidence:(1–3,8,367–369)

Sucrose

Use:

- Analgesia for procedural pain in babies.

Dose and route:

By mouth:

- **Neonate over 32 weeks**: 0.5-2ml of 24% sucrose orally 2 minutes before the procedure (alternatively a pacifier/dummy could be placed in the sucrose solution).

  Incremental doses 0.1ml can be used up to the maximum of 2ml. Multiple doses can be given during a single procedure.

- **Preterm infants**: administer a maximum of 4 times per 24 hours
- **Neonates and babies**: administer a maximum of 8 times in 24 hours

Notes

Licensing

- Algopedol® is licensed for use in term and preterm infants less than 4 months of age

Therapeutics

- Dextrose 25% in similar volumes may achieve the same effect.
- Effect enhanced when combined with other non-pharmacological techniques for providing analgesia including non-nutritive sucking and behavioural measures such as swaddling.
- Limited evidence to guide dosing in very premature babies
- May have a role in managing pain in infants up to 12 months.
- Sucrose given orally, for procedural pain management within the recommended dosing, does not alter blood glucose levels.
- Neonates and infants of mothers maintained on methadone may have altered endogenous opiate systems, resulting in a lack of analgesic effect of oral sucrose in the first days to weeks of life.

Contraindications, cautions

- Contraindicated in babies with oesophageal atresia, tracheo-oesophageal fistula, confirmed or suspected intra-abdominal pathology (e.g. NEC), fructose intolerance.
- Use with caution in infants with altered gag or swallow reflex or swallowing problems, cardio-respiratory instability or any major GI pathology.

Administration

- Oral administration using vial dispenser directly onto the anterior portion of the tongue. If needed, the vial can be closed and laid flat after first opening and be used again in the same infant within a period of 8 hours.
- Infants who are nil by mouth (NBM) or have an endotracheal tube in situ can (with medical approval) have the dose of oral sucrose applied with a small swab directly onto the tongue.
- Not appropriate for administration via feeding tube

Available as

- Preservative-free oral solution of sucrose 24% (Algopedol®) in 2 ml vials for single patient use, or sucrose 24% (Sweet-Ease) in 15ml cups which can be used to dip a pacifier into or draw up into dropper/syringe.

Evidence: (11,370–373)

Tapentadol

Use:

- Opioid analgesic

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

Pain in opioid naïve patients

By mouth using immediate release preparations

- **Child 2-17 years and body-weight over 16 kg:** 1.25mg/kg/dose every 4 hours. Maximum initial dose 50mg, can be increased to body-weight adjusted dose for subsequent dosing

  The dose for children with a high BMI must not exceed the calculated dose for a body-weight at the 97.5 percentile for the given age.

  Maximum total daily dose 7.5mg per kg body-weight (*see notes below)

- **18 years and older**: Initially 50mg every 4–6 hours, adjusted according to response, on the first day of treatment, an additional dose of 50mg may be taken 1 hour after the initial dose; maximum 700mg in the first 24 hours; maximum 600mg daily.

By mouth using modified release preparations

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

Notes:

- Opioid analgesic. Approximately 3 times less potent than morphine i.e.50mg oral tapentadol is approximately equivalent to 15mg oral morphine

Licensing

- Tapentadol oral solution is licensed for the relief of moderate to severe acute pain in children from 2 years of age (>16 kg body-weight) for a maximum of 72 hours. Use of tablet formulations or for treatment of chronic pain or for a duration >72 hours in children is off-label. Data on safety and efficacy of long-term use in children is not yet available and clinical trials are on-going.
- Tapentadol oral solution, immediate-release and modified-release tablets are licensed in adults for treatment of moderate to severe acute and chronic pain.

Therapeutics

- Dual action centrally acting opioid analgesic; agonist at the 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.
- 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).
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Cautions

- MHRA/CHM advice: Tapentadol (Palexia): risk of seizures and reports of serotonin syndrome when co-administered with other medicines (January 2019). Tapentadol can induce seizures and should be prescribed with caution in patients with a history of seizure disorders or epilepsy. Seizure risk may be increased in patients taking other medicines that lower seizure threshold, for example, antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics.

Side effects

- Potential adverse effects as for other opioids. However GI side effects are reportedly less than with oxycodone or morphine.

Hepatic and renal impairment

- Dosage adjustment is not required in mild or moderate renal impairment. not recommended in severe renal impairment (lack of clinical trial data).
- Dosage adjustment is not required in mild hepatic impairment. Reduce initial dose in moderate hepatic impairment. Not recommended in severe hepatic impairment (lack of clinical trial data).

Pharmacokinetics

- Based on immediate release tablets-onset of action is less than 1 hour with time to peak serum concentrations around 75 minutes. Duration of action 4-6 hours. Duration of action of modified-release tablets is 12 hours.
- Tapentadol is rapidly and completely absorbed after oral administration. However mean absolute bioavailability after a single-dose administration is ~32% due to extensive first-pass metabolism.
- The major elimination pathway for tapentadol is glucuronide conjugation. Tapentadol does not have any active metabolites.

Administration

- Tapentadol oral solution 20mg/ml can be taken undiluted or diluted in water or any non-alcoholic drink. Use the dosing pipette (5ml subdivided in 0.1ml (2mg) intervals) provided to ensure the exact dose can be accurately measured.
- Tapentadol oral solution can be administered via an enteral feeding tube. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.
- Tapentadol oral solution contains 2mg/ml propylene glycol.
- Modified-release tapentadol tablets should be swallowed whole; crushing or chewing will lead to a rapid release of an overdose of tapentadol.

Available as

- Oral solution 20mg/ml (licensed from 2 years) Palexia®, immediate-release tablets 50mg, 75mg (licensed from 18 years only) Palexia®, Modified-release tablets (licensed from 18 years only) 25mg, 50mg, 100mg, 150mg, 200mg, 250mg Palexia®, Ationdo®. Modified-release capsules (licensed from 18 years only) 50mg, 100mg, 150mg, 200mg, 250mg Tapimio® As for all modified release opioids, brand prescribing is recommended to reduce the risk of confusion and error in dispensing and administration

CD

- CD Schedule 2

Evidence: (2,3,374–381)

Temazepam

Use:

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

Important safety information

For all benzodiazepines

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and route:

By mouth:

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

Notes:

- GABA mimetic, anxiolytic sedative.

Licensing

- Tablets not licensed for use in children.

Therapeutics

- Correct contributory factors to insomnia if possible. Use in association with non-pharmacological methods.

Side effects

- Can cause paradoxical increased hostility and aggression requiring dose adjustment. Can also paradoxically increase anxiety. May impair judgement and reaction time.

Contraindications, cautions

- Contraindicated in severe hepatic impairment (unless in imminently dying)
- Caution in renal impairment, shorter half-life benzodiazepines may be preferable
- Contraindicated in respiratory depression, compromised airway and untreated sleep apnoea syndrome, except in the imminently dying.

Pharmacokinetics

- Oral bioavailability at least 90%; peak plasma concentration within 50 minutes of oral administration. Long plasma half-life of 8-15 hours.

Administration

- Oral solution may be administered via an enteral feeding tube. If administered via the jejunum monitor for loss of efficacy or increased side effects.

Available as

- Tablets (10mg, 20mg) and oral solution (10mg/5 ml).

CD

- Schedule 3 controlled drug (CD No register).

Evidence:(1–3,8)

Tizanidine

Use:

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

Dose and route:

By mouth

- **Child 18 months-6 years**: 1mg/day in divided doses; increase if necessary, according to response.
- **7-11 years**: 2mg/day in divided doses; increase if necessary, according to response.
- **12 years and over**: 2mg/day in divided doses increasing in increments of 2mg at intervals of 3–4 days

  Usual adult total daily dose 24mg. Maximum total daily dose 36mg.

Administer as 3-4 divided doses. Timing and frequency of dosing is specific to individual patient as maximum effect is seen 2-3 hours after administration.

Titrate doses slowly over 2-4 weeks to reduce side effects

Notes:

Licensing

- Not licensed for use in children.

Therapeutics

- Limited research evidence in children. Paediatric doses largely extrapolated from adult doses
- Usually prescribed and titrated by neurologists.
- Peak response not seen until approximately 8 weeks.
- Avoid abrupt withdrawal-risk of rebound hypertension and tachycardia.

Contraindications, cautions

- Use with caution with drugs known to prolong the QT-interval.

Monitoring

- Monitor liver function monthly for first 4 months.

Side effects

- Drowsiness, weakness, hypotension and dry mouth are common side effects.

Hepatic impairment, renal impairment

- Use with caution in liver disease, monitor liver function regularly.
- Caution in renal impairment

Interactions

- Metabolised by cytochrome P450 enzyme CYP1A2. Levels increased by drugs that inhibit this enzyme including ciprofloxacin and possibly famotidine potentially leading to severe hypotension. Levels may be reduced by drugs that induce this enzyme including phenytoin.

Administration

- Tablets may be crushed and administered in water if preferred. May be administered via an enteral feeding tube. Tablets do not disperse readily, but will disintegrate if shaken in 10 ml of water for 5 minutes. The resulting dispersion will flush via an 8Fr NG tube without blockage. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

Available as

- Tablets (2mg, 4mg).

Evidence: (2,3,8,382–385)

Tramadol

Use:

- Weak opioid with additional non-opioid analgesic actions

The WHO now advises there is insufficient evidence to make a recommendation use of weak opioids in children and recommends moving directly from non-opioids to low dose strong opioids for the management of moderate uncontrolled pain in children

Important safety information

For all opioids

MHRA/CHM advice: Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression (March 2020)

The MHRA reminds healthcare professionals that opioids co-prescribed with benzodiazepines and benzodiazepine-like drugs can produce additive CNS depressant effects, thereby increasing the risk of sedation, respiratory depression, coma, and death.

The APPM recognises that in paediatric palliative care co-prescription of opioids and benzodiazepines is frequently necessary and appropriate. In these circumstances the lowest effective doses should be used. Doses should be increased gradually wherever possible, changing the dose of only one drug at a time, and allowing sufficient time for the changes to take effect before making further dose adjustments.

Dose and routes

By mouth, subcutaneous, intramuscular or slow intravenous injection:

- **Child 4-11 years**: 1mg/kg/dose every 6 hours. Maximum 50mg/dose.

  Increased if required to 1.5mg/kg/dose every 6 hours and then to 2mg/kg/dose every 6 hours. Maximum 100mg/dose

- **12 years and over**: Initial dose of 50mg every 4-6 hours. Increase if necessary to a maximum of 400mg/day given in divided doses every 4-6 hours.

Total daily dose can also be given as a continuous intravenous or subcutaneous infusion/24hours.

Notes:

Licensing

- Not licensed for use in children under 12 years.

Therapeutics

- By mouth tramadol is approximately 1/10 as potent as morphine. However equianalgesic ratios may be unreliable due to inter-individual variation in CYP2D6 activity.
- Has been given by sublingual route at similar doses
- May be helpful in neuropathic pain and visceral hyperalgesia
- Tramadol itself has analgesic properties. It is also metabolized in the liver by CYP2D6 to the active metabolite desmethyltramadol which has a higher affinity for the mu-opioid receptor. Unlike codeine, poor metabolisers experience only slightly diminished analgesic effect. The risk of respiratory depression may be higher in the 5% of the western European population who are ultra-metabolisers. However, the risk is likely to be significantly less than with codeine.
- Refer to Principles of Opioid Stewardship, Appendix 2
- Ensure access to an appropriate stimulant laxative if administered regularly

Side effects

- Causes less constipation and respiratory depression than the equivalent morphine dose. Risk of respiratory depression may be increased in paediatric patients who are obese or have conditions such as obstructive sleep apnoea or severe lung disease, or who are ultrarapid metabolizers of the drug
- Side effects include diarrhoea, retching, fatigue and paraesthesia.

Pharmacokinetics

- Onset of action after an oral dose is 30 to 60 minutes. Duration of action is 4-6 hours.

Interactions

- Analgesic effect may be reduced by ondansetron. Increased risk of serotonin syndrome with co-administration of tramadol and ondansetron

Hepatic impairment, renal impairment

- Avoid or reduce dose

Administration

- Orodispersible tablets should be sucked and then swallowed or they may be dispersed in water. Modified release capsules may be opened and the capsule contents swallowed immediately without chewing.
- Soluble or orodispersible tablets may be dissolved in water for administration via an enteral feeding tube or use the oral drops or disperse capsule contents. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.
- For subcutaneous infusion dilute in sodium chloride 0.9% or water for injection

Patient information

- Patient information see Medicines for Children leaflet “Tramadol for pain” https://www.medicinesforchildren.org.uk/medicines/tramadol-for-pain/

Available as

- Soluble tablets 50mg, Orodispersible tablets 50mg, Immediate release capsules 50mg, Oral solution 10mg/ml, oral drops 100mg/ml, modified-release 12hr tablets 50mg, 100mg, 150mg, 200mg, 300mg, 400mg, modified release 12hr capsules 50mg, 100mg, 150mg, 200mg, modified-release 24hr tablets 150mg, 200mg, 300mg, 400mg, solution for injection 100mg/2ml

- Brand prescribing of modified release preparations is recommended to reduce the risk of confusion and error in dispensing and administration. Care with prescribing preparations due to availability of both 12-hour and 24 hour modified release formulations

CD

- Schedule 3 CD

Evidence: (1,2,8,10,61–63,120,187,386–393)

Tranexamic acid

Use:

- Inhibition of fibrinolysis
- Oozing of blood (e.g. from mucous membranes or capillaries), particularly when due to thrombocytopenia or platelet dysfunction
- Menorrhagia

Dose and route:

Inhibition of fibrinolysis

By mouth:

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

By intravenous injection over at least 10 minutes:

- **Child 1 month and over**: 10mg/kg (maximum dose 1 g) 2-3 times daily.

By continuous intravenous infusion:

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

Menorrhagia

By mouth:

- **Child 12 years and over**: 1g 3 times daily for up to 4 days.

  Up to 4g in divided doses can be used for very heavy bleeding. Treatment should not be initiated until menstruation has started.

Prevention or treatment of oral bleeding

For use as mouthwash (5% solution):

- **Child 6 years and over**: 5-10ml 4 times daily for 2 days. Not to be swallowed.

Topical treatment of bleeding:

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

Notes:

Licensing

- Injection not licensed for use in children under 1 year or for administration by intravenous infusion.

Side effects

- Urinary tract clots resulting from use in presence of haematuria can result in urinary tract obstruction and clot 'colic'
- Diarrhoea, nausea and vomiting

Hepatic impairment, renal impairment

- Reduce dose in mild to moderate renal impairment and avoid in severe renal impairment.

Administration

- For administration via an enteral feeding tube, the oral suspension (unlicensed) or injection solution is preferred. Tablets may be dispersed in water for tube administration without blockage. No specific information for jejunal administration.
- Parenteral preparation can be used topically.

Patient information

- See Medicines for Children leaflet "Tranexamic acid for heavy bleeding during periods" https://www.medicinesforchildren.org.uk/medicines/tranexamic-acid-for-heavy-bleeding-during-periods/ and Medicines for Children leaflet "Tranexamic acid for the treatment or prevention of bleeding in haemophilia and other clotting problems"
- https://www.medicinesforchildren.org.uk/medicines/tranexamic-acid-for-the-treatment-or-prevention-of-bleeding-in-haemophilia-and-other-clotting-problems/

Available as

- Tablets (500mg), syrup (500mg/5 ml available from 'specials' manufacturers) and injection (100mg/ml ampoules). Mouthwash only as extemporaneous preparation.

Evidence: (1–3,394)

Trihexyphenidyl

Uses:

- Dystonia
- Sialorrhoea (drooling)
- Antispasmodic.

Dose and route:

By mouth

- **Child 3 months and over**: 1–2mg daily in 1-2 divided doses, increased every 3-7 days by 1mg daily; adjusted according to response and side effects, maximum 2mg/kg (or 100mg) daily

  Doses needed to control drooling are generally much lower than those needed for dystonia

Notes:

- Reduces the effects of the relative central cholinergic excess that occurs in dopamine deficiency.

Licensing

- Not licensed for use in children.

Therapeutics

- Use in conjunction with careful observation and a full non-drug management programme including positioning, massage, holding, distraction, checking for causes of exacerbations etc. Seek specialist neurological advice.
- May have limited efficacy in children with cerebral palsy and dystonia.
- Start at a low dose and increase gradually to minimise the incidence and severity of side effects.
- May take several weeks for maximal effect on dystonic movements to be seen.
- Do not withdraw abruptly in children who have been on long-term treatment.

Contraindications, cautions

- Contraindicated in myasthenia gravis

Side effects

- Side effects are very common. Mouth dryness, constipation, blurring of vision, dizziness and nausea can occur in 30-50% patients. Less common side effects include urinary retention, tachycardia, confusion, insomnia and with very high doses CNS disturbance including oculogyric crisis

Hepatic impairment, renal impairment

- Use with caution in children with renal or hepatic impairment.

Pharmacokinetics

- Onset of action is usually within 1 hour, maximum effect occurs within 2-3 hours and duration of effect approximately 6-12 hours.

Administration

- Tablets may be crushed and mixed in soft food.
- Administration with or after food may help minimise gastrointestinal adverse effects
- The oral liquid may be used for administration via feeding tubes. Alternatively the tablets will disperse readily in water. No specific data for jejunal administration: suggest administering as for gastrostomy and monitoring for increased side effects or loss of efficacy.

Patient information

- See Medicines for Children leaflet “Trihexyphenidyl hydrochloride for dystonia” https://www.medicinesforchildren.org.uk/medicines/trihexyphenidyl-hydrochloride-for-dystonia/

Available as

- Tablets 2mg and 5mg; oral liquid 5mg in 5 ml.

Evidence: (1,2,8,39,58,81,158,395)

Vitamin K (Phytomenadione)

Use:

- Treatment of haemorrhage associated with vitamin-K deficiency (seek specialist advice)
- Reversal of coumarin anticoagulant (warfarin) overdose

Dose and route:

By mouth or intravenous:

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

Notes:

Contraindications, cautions

- Caution with intravenous use in premature infants less than 2.5 kg, increased risk of kernicterus

Administration

- Risk of cardiovascular collapse with rapid administration. Preferably dilute with Glucose 5% and give over 15-20 minutes. Can also be given as a slow intravenous injection over 3-5 minutes
- Injection should be protected from the light.

Available as

- Capsules 1mg, oral drops 200 micrograms/ml and injection 10mg/ml. Many other forms and strengths available from special order manufacturers.

Evidence: (1,2)

Appendices

1. Opiate conversion tables

- Opioid conversion tables can be used to calculate approximate equianalgesic doses of opioids when switching from a weak opioid to morphine, or from one strong opioid to another.
- Caution is *always* necessary. Conversion ratios are never more than an approximate guide due to:
    - Wide inter-individual variation in opioid pharmacokinetics
    - Limited data on opioid equi-analgesia in children
    - Differences between opioid pharmacokinetics in adults and children
    - Data largely derived from single dose studies
    - Potential for opioid tolerance related to dose and duration of opioid treatment
    - Direction of switch in opioid
    - Concurrent medications
- If switching from an opioid other than morphine to another opioid, convert the dose of the first opioid to morphine equivalent, and then use that quantity to determine the dose of the second opioid.
- Consider reducing the dose of the new opioid by 25-50% when rotating opioids due to intolerable side effects or lack of efficacy. This is especially important if the patient is already on a high dose of the previous opioid, or there has recently been rapid dose escalation.

Notes

- Equianalgesic ratios for methadone are dose dependent and highly variable: see methadone monograph
- Mean oral bio-availability of oxycodone is 75% (range 60–87%). For safety, recommended equianalgesic ratios are therefore either rounded down to 1.5:1 or up to 2:1 depending on direction of switch and rounding errors
- Newer systematic review evidence suggests using a ratio of 3:1 when converting morphine from oral to intravenous morphine
- Bioavailability of some drugs may be lower for subcutaneous versus intravenous administration, particularly for infusions. However the APPM recommendation is to assume similar pharmacokinetics for intravenous and subcutaneous dosing.
- Oral tapentadol is approximately 3 times less potent than morphine e.g. 30mg tapentadol is approximately equivalent to 10mg oral morphine. However experience in children is currently too limited to make clear recommendations regarding opioid conversion

Evidence: (1–3,117,117,396,397)

Conversion from oral morphine

Conversion		Ratio	Calculation	Example
From	**To**			
Morphine oral	Alfentanil CSCI or CIVI	30:1	Divide 24hour morphine dose by 30	Morphine oral 60mg/24hours ÷ 30 = alfentanil CSCI 2mg/24hours
Morphine oral	Buprenorphine sublingual	80:1	Divide 24hour morphine dose *in mg* by 80 to give 24hour buprenorphine dose *in mg* Then multiply 24hour buprenorphine dose *in mg* by 1,000 to give 24hour buprenorphine dose *in micrograms* *Then* divide 24hour buprenorphine dose *in micrograms* into 3 or 4 divided doses for 8 or 6 hourly administration	Morphine oral 60mg/24hours ÷ 80 = buprenorphine SL 0.75mg/24hours Buprenorphine 0.75mg/24hours x 1000 = buprenorphine 750micrograms/24hours Buprenorphine 750micrograms/24hours ÷ 3 = 250micrograms 8 hourly *Round down* to 200micrograms SL 8 hourly
Morphine oral	Buprenorphine transdermal	100:1	Divide 24hour morphine dose *in mg* by 100 to give 24hour buprenorphine dose *in mg* *Then* multiply 24hour buprenorphine dose *in mg* by 1,000 to give 24hour buprenorphine dose *in micrograms* *Then* divide 24hour buprenorphine dose in micrograms by 24 to give patch strength in micrograms/hour	Morphine oral 300mg/24hours ÷ 100 = buprenorphine transdermal 3mg/24hours Buprenorphine 3mg/24hours x 1000 = buprenorphine 3,000micrograms/24hours Buprenorphine 3,000micrograms/24hours ÷ 24 = buprenorphine 125micrograms/hour *Round down* to 70+35microgram/hour buprenorphine patches
Morphine oral	Diamorphine CSCI or CIVI	6:1	Divide 24hour morphine dose by 6	Morphine oral 30mg/24hours ÷ 6 = diamorphine CSCI 5mg/24hours
Morphine oral	Diamorphine intranasal	3:1	Divide PRN morphine dose by 3	Morphine oral 3mg PRN ÷ 3 = Diamorphine intranasal 1mg PRN

Conversion from oral morphine

Conversion		Ratio	Calculation	Example
From	**To**			
Morphine oral	Fentanyl CSCI or CIVI	100:1[a]	Divide 24hour morphine oral *in mg* dose by 100 to give fentanyl dose in *mg/24hours* *Then* multiply fentanyl dose in mg/24hours by 1000 to convert to *micrograms/24hours*	Morphine oral 60mg/24hours ÷ 100 = fentanyl CIVI 0.6mg/24hours CSCI Fentanyl CIVI 0.6mg/24hours x 1000 = fentanyl CIVI 600micrograms/24hours
Morphine oral	Fentanyl transdermal patch	100:1	Divide 24hour morphine oral dose by *in mg* 100 to give fentanyl transdermal dose in mg *Then* multiply by 1,000 to give fentanyl transdermal dose in micrograms *Then* divide by 24 to give fentanyl transdermal dose in micrograms/hour	Morphine oral 90mg/24hours ÷ 100 = fentanyl transdermal 0.9mg/24hours Fentanyl 0.9mg/24hours x 1000 = fentanyl 900micrograms/24hours Fentanyl 900micrograms/24hours ÷ 24 = fentanyl 37.5mg/hour = fentanyl 12+25micrograms/hour patches
Morphine oral	Hydromorphone oral	5:1	Divide morphine oral dose by 5	Morphine oral 10mg ÷ 5 = hydromorphone oral 2mg
Morphine oral	Oxycodone oral	2:1	Divide morphine oral dose by 2	Morphine oral 20mg ÷ 2 = oxycodone oral 10mg
Morphine oral	Oxycodone CSCI or CIVI	3:1	Divide morphine oral dose by 3	Morphine oral 30mg/24hours ÷ 3 = oxycodone CSCI or CIVI 10mg/24hours
Morphine oral	Tramadol oral	1:10	*Multiply* the total daily dose of oral morphine by 10	Morphine oral 10mg **x**10 = tramadol oral 100mg

[a] Some centres use equianalgesic ratio of 150:1 depending on circumstances

Conversion from continuous intravenous or subcutaneous morphine

Conversion		Ratio	Calculation	Example
From	**To**			
Morphine CSCI or CIVI	Alfentanil CSCI or CIVI	15:1	Divide 24hour morphine dose by 15	Morphine CSCI 30mg/24hours ÷ 15 = alfentanil CSCI 2mg/24hours
Morphine CSCI or CIVI	Diamorphine CSCI or CIVI	2:1	Divide 24hour morphine dose by 2	Morphine CSCI 15mg/24hours ÷ 2 = diamorphine CSCI 7.5mg/24hours
Morphine CSCI or CIVI	Fentanyl CSCI or CIVI	50:1[a]	Divide 24hour morphine dose by 50 to give fentanyl dose in *mg/24hours* *Then* multiply fentanyl dose in mg/24hours by 1000 to convert to *micrograms/24hours*	Morphine CIVI 25mg/24hours ÷ 50 = fentanyl CIVI 0.5mg/24hours Fentanyl CIVI 0.5mg/24hours x 1000 = 500micrograms/24hours
Morphine CSCI or CIVI	Fentanyl patch	50:1	Divide 24hour morphine dose by 50 to give fentanyl dose in *mg/24hours* *Then* multiply fentanyl dose in mg/24hours by 1000 to convert to *micrograms/24hours* *Then* divide by 24 to convert to micrograms/hour	Morphine CSCI 30mg/24hours ÷ 50 = fentanyl transdermal 0.6mg/24hours Fentanyl 0.6mg/24hours x 1000 = 600micrograms/24hours Fentanyl CIVI 600micrograms/24hours ÷ 24 = 25micrograms/hour patch
Morphine CSCI or CIVI	Hydromorphone CSCI or CIVI	5:1	Divide 24hour morphine dose by 5	Morphine CSCI 25mg ÷ 5 Hydromorphone CSCI =5mg
Morphine CSCI or CIVI	Oxycodone CSCI or CIVI	1:1	Use the same dose	Morphine CSCI 50mg/24h = oxycodone CSCI 50mg/24hours

[a] Some centres use equianalgesic ratio of 75:1 depending on circumstances

Change of route

Conversion		Ratio	Calculation	Example
From	**To**			
Buprenorphine sublingual	Buprenorphine IV or SC *bolus*	2:1	Divide sublingual buprenorphine by 2	Buprenorphine SL 200micrograms ÷ 2 = buprenorphine SC bolus 100micrograms
Diamorphine intranasal	Diamorphine IV or SC bolus	2:1	Divide intranasal diamorphine by 2	Diamorphine intranasal 2mg ÷ 2 = Diamorphine intravenous 1mg
Hydromorphone oral	Hydromorphone CSCI or CIVI	2:1[a]	Divide 24hour hydromorphone dose by 2	Hydromorphone oral 10mg ÷ 2 = hydromorphone CSCI 5mg
Morphine oral	Morphine CSCI or CIVI	3:1	Divide 24hour morphine oral dose by 3	Morphine oral 15mg ÷ 3 = morphine CSCI 5mg
Methadone oral	Methadone CIVI or CSCI	2:1	Divide 24hour methadone dose by 2	Methadone oral 2mg ÷ 2 = methadone CSCI 1mg
Oxycodone oral single dose	Oxycodone SC or IV bolus single dose	1.5:1	Divide oxycodone oral dose by 1.5	Oxycodone oral 4.5mg ÷ 1.5 = oxycodone IV/SC *bolus* 3mg
Oxycodone oral	Oxycodone CSCI or CIVI	1:5:1[b]	Divide 24hour dose of oral oxycodone by 1.5	Oxycodone oral 90mg/24hours ÷1.5 = oxycodone CSCI 60mg/24hours
Tramadol oral	Tramadol CIVI or CSCI	1:1	Use the same dose	Tramadol oral 10mg/24hours = tramadol CSCI 10mg/24hours

[a] Some centres use equianalgesic ratio of 3:1 depending on circumstances

[b] Some centres use a equianalgesic ratio of 2:1 for infusions

2. Opioid stewardship

- Opioids are high-risk medicines which are widely used in the field of paediatric palliative care. The concept of opioid stewardship is based on the principles of antibiotic stewardship in that opioids should be used for the right patient in the right way at the right time. Recent evidence shows an increasing trend in global opiate use which has seen a corresponding increase in harm. Opioid stewardship entails a set of systematic and coordinated interventions designed to improve the health of and minimise harm to our patients.
- Key aspects to opiate stewardship that should be followed include:
    - Patient information gathering and shared decision making
    - Effective communication with the patient or their proxy and between members of the multidisciplinary team
    - Thorough assessment and regular re-assessment of the indication(s) for opioid therapy
    - Risk-benefit analysis
    - Appropriate prescribing and dispensing, ideally by a single prescribing team.
    - Monitoring and management of opioid adverse effects
    - Clear documentation
    - Regular review of therapy
    - Appropriate storage
    - Disposal of unused opioids

Evidence (398)

3. Prolonged QT syndrome

- Polypharmacy in paediatric palliative care is common. Therefore prescribers must be aware of potential risks, including prolongation of the QT-interval. This is particularly relevant to paediatric patients receiving palliative care where there may be additional risk factors for prolonged QTc including cardiac abnormalities, hypothyroidism, familial long QT syndrome, electrolyte imbalance or taking other drugs known to prolong the QT-interval
- Although the frequency of serious life-threatening arrhythmias, including Torsades de pointes (TdP), in this population appears to be low, it should be considered carefully when prescribing medications known to prolong QTc.

Drugs associated with prolonged QT-interval

- Drugs that may affect the QT-interval can be subdivided into four categories

    1. Known risk of serious life-threatening arrhythmias -These drugs prolong the QT-interval AND are clearly associated with a known risk of TdP, even when taken as recommended.
    2. Possible risk of TdP-These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.
    3. Conditional risk of TdP-These drugs are associated with TdP BUT only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalaemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).
    4. Drugs to avoid in congenital long QT syndrome (cLQTS)-These drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories PLUS additional drugs that do not prolong the QT-interval per se but which have a special risk because of their other actions.

- Drugs in group 1, (as of July 2023*) but not those in the other categories* are identified in the notes section of the relevant monograph in the formulary. However the list of drugs associated with prolonged QT-interval is being continually updated. Professionals are strongly advised to check the most up to date list on https://www.crediblemeds.org/ when prescribing or advising on prescribing for patients at increased risk of prolonged QT-interval

Safe prescribing

- When prescribing drugs which are known to prolong the QT-interval it is important to gather information about any additional risk factors in order to make an informed decision about the risks and benefits of the proposed drug.
- Co-administration of two or more drugs that prolong the QTc should be avoided where possible.
- For high risk patients consider a 12 lead ECG before starting treatment and repeating once the medication has reached steady state.

Evidence: (222,227,399,400)

4. Benzodiazepines

Approximate equivalent oral anxiolytic sedative doses[ab]

Benzodiazepine	Approximate equivalent oral dose
Clobazam	10mg
Clonazepam	250micrograms
Diazepam	5mg
Lorazepam	500micrograms
Midazolam	2.5mg[b] *intravenous or subcutaneous*
Temazepam	10mg

Comparative pharmacokinetic data

Diazepam[a]

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

[a] BNF 85: March-September 2023. London: Pharmaceutical Press; 2023.

[b] Charlesworth S, Howard P, Wilcock A, editors. PCF8: palliative care formulary. Eighth edition. London: Pharmaceutical Press; 2022.

[c] Medicines for Children 2003

Lorazepam[a]

	Bioavailability	Onset of action (minutes)	Time to peak plasma concentration (minutes)	Duration of action (hours)	Half-life (hours) (including active metabolites)
Lorazepam sublingual		5	150		
Lorazepam oral	90%[a,b]	10-15	150 120[b]	6-72 8[b]	10-20[a,b]
Lorazepam intravenous		2-5[b] 10		4-6[b]	12-16

Midazolam[a,b]

	Bioavailability	Onset of action (minutes)	Time to peak plasma concentration (minutes)	Duration of action (hours)	Half-life (hours) (including active metabolites)
Midazolam buccal	85% 75%[c]	15 5[b]	≤30		
Midazolam oral	40%	20-30 10-30[b]	30-60	<4 20-90[3] minutes	1-4 2-5 [a,b]
Midazolam Sub-cutaneous	95%	5-10	30		
Midazolam intravenous		2-3[a,b]		30-60mins[b]	

[a] Charlesworth S, Howard P, Wilcock A, editors. PCF8: palliative care formulary. Eighth edition. London: Pharmaceutical Press; 2022

[b] Medicines for Children 2003

[c] Kienitz R et al. Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 2022 Sep;36(9):951–75.

5. Gabapentin to pregabalin switch

- Gabapentin and pregabalin have similar mechanisms of action. However, gabapentin absorption is saturable, leading to non-linear pharmacokinetics, whereas pregabalin possesses linear pharmacokinetics. Furthermore, clearance of pregabalin is faster in children under 30 kg and particularly those under 6 years of age. Higher doses and/or more frequent dosing interval may therefore be needed. As a consequence, switching between gabapentin and pregabalin is not straight-forward.

- There is limited evidence in the literature with regard to managing a switch, with no evidence in children. However many pain centres in the UK have developed local protocols for a switch in adults, with no reports of adverse effects. The following conversion factors have been used:
    - 1/6 is generally accepted as a standard conversion however a range of factors from 1/4 to 1/9 have been used to accommodate practical dosing schedules
    - Lower conversion factors of 1/6 to 1/9 used for higher gabapentin dosing to accommodate the non-linear kinetics of gabapentin
- The table below details a switch from gabapentin to pregabalin for neuropathic pain in children extrapolated from available adult data. Conversion factors allow for practical dosing.

Table 2: Gabapentin to Pregabalin switch

<table>
<tr><th>Age</th><th>Gabapentin
APPM formulary dose</th><th>Recommended conversion ratio[a]</th><th>Pregabalin
APPM formulary dose</th><th>Recommended initial maximum pregabalin dose</th></tr>
<tr><td>1-23 months</td><td>5-10mg/kg/dose
3 times daily</td><td>1/6</td><td>1-5mg/kg/dose
2 times daily</td><td>5mg/kg/dose
2 times daily</td></tr>
<tr><td>2-11 years</td><td>5-30mg/kg/dose
3 times daily</td><td>1/6</td><td>1-5mg/kg/dose
2 times daily</td><td>5mg/kg/dose[b]
2 times daily
Maximum 100mg/dose</td></tr>
<tr><td rowspan="3">12 years and over</td><td>300mg
3 times daily</td><td>1/5</td><td rowspan="3">12-15 years
1-5mg/kg/dose
2 times daily
16 years and over
75mg-300mg
2 times daily</td><td>100mg
2 times daily</td></tr>
<tr><td>400mg
3 times daily</td><td>1/6</td><td>100mg
2 times daily</td></tr>
<tr><td>600mg-1.2g
3 times daily</td><td>1/6-1/9</td><td>200mg
2 times daily</td></tr>
</table>

[a] From adult literature and taking into account recommended doses of gabapentin and pregabalin in neonates and children
[b] Children with body-weight less than 30Kg and especially those under 6 years may require up to 15mg/kg/24hours, giving a conversion ratio that may be as much as 1/3

- Using the table:
    1. Calculate the child's total daily gabapentin dose in mg/24hours
    2. Multiply by the relevant conversion ratio to get the approximate equivalent dose of pregabalin in mg/24hours. Divide the total daily dose of pregabalin by two for twice daily administration
    3. The dose of pregabalin would be expected to fall within the range given in the formulary and should not exceed the recommended initial maximum dose

Evidence (3,401–406)

6. Buccal administration of liquid preparations

- Buccal or sublingual administration is increasingly accepted as a convenient, painless method of drug delivery. Potential advantages of administration by these routes include rapid absorption without the need to swallow and by-passing first pass metabolism. Absorption of drugs via the buccal or sublingual routes is influenced by a number of important factors with the potential for differences in bioavailability between patients and in the same patient over time.
- Factors affecting absorption via buccal or sublingual routes
  - Volume of the oral cavity
  - pH of the oral cavity
  - Rate of saliva production
  - Site of drug delivery: the sublingual mucosa has higher permeability than the buccal mucosa but small volume for administration
  - Relative lipophilic (transcellular absorption) versus hydrophilic (paracellular absorption) properties of the molecule
  - Molecular size: molecules (molecules greater than 500 Da are unlikely to be absorbed)
  - Excipients
  - Volume of administration
  - Ability to swallow or co-operate with not swallowing
  - Palatability
- The volume of liquid preparation that can be tolerated in the buccal or sublingual cavity without swallowing has been estimated as 2ml in adult patients. No equivalent data exists for children and extrapolating to the paediatric population is complex. The table below provides approximations based on scaling by weight, body surface area and head circumference. In general liquid preparations for buccal or sublingual administration should be administered in the smallest measurable volume

Age range	Estimated maximum volume for buccal or sublingual administration
Neonate -11 months	0.5ml
1-5 years	1ml
6-10 years	1.5ml
11 years and over	2ml

Evidence: (121,407–409)

7. Dosing in obesity

- Patients requiring paediatric palliative care are frequently atypical in terms of weight for age or body composition. Childhood obesity, defined as body weight greater than or equal to the 98th centile for age, is increasing. Even patients who are seemingly a normal weight for age may have relatively more body fat and less lean muscle mass if they are almost completely and permanently immobile and non weight-bearing.
- Children are usually dosed according to their body-weight or age, as a surrogate of 'normal' size and function. However, in children with obesity there is a risk of drug overdose if total body weight is used. Therefore, for a small selection of drugs it is recommended to use either ideal body weight (IBW) or adjusted body weight (AdjBW))

Weight (kg)	Definition
Total Body Weight (TBW)	Weight in kg (no adjustment necessary)
Ideal Body Weight (IBW)	Cross reference height centile to weight for that centile If height is not available, use length or arm span.
Adjusted Body Weight (AdjBW)	IBW + Adjustment Factor (0.3) x (TBW-IBW)

Analgesics

- Fentanyl (AdjBW)
- Ibuprofen (AdjBW)
- Morphine (IBW)
- Paracetamol (AdjBW)

Anticonvulsants

- Carbamazepine (IBW)
- Levetiracetam (maintenance) (AdjBW)
- Phenytoin (maintenance) (AdjBW)

Evidence: (410)

References

1. BNF for children: 2022-2023. London: Pharmaceutical Press; 2022.

2. BNF 85: March-September 2023. London: Pharmaceutical Press; 2023.

3. Charlesworth S, Howard P, Wilcock A, editors. PCF8: palliative care formulary. Eighth edition. London: Pharmaceutical Press; 2022.

4. Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol. 2016 Jan;15(1):78–91.

5. Shinnar S, Gammon K, Bergman EW Jr, Epstein M, Freeman JM. Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts. J Pediatr. 1985 Jul;107(1):31–7.

6. Moffett BS, Kulik K, Khichi M, Arikan A. Acetazolamide-Associated Acute Kidney Injury in Critically Ill Pediatric Patients. J Pediatr Pharmacol Ther. 2021 Jul 1;26(5):467–71.

7. Incecik F, Ozcan N, Ozcanyuz DG, Mert GG. Acetazolamide-Induced Agranulocytosis in a Patient with Pseudotumor Cerebri. Ann Indian Acad Neurol. 2020;23(5):732–3.

8. White R, Bradnam V. Handbook of drug administration via enteral feeding tubes. 3. ed. London: Pharmaceutical Press; 2015. 732 p.

9. Asiedu MN, Mejia GL, Hubner CA, Kaila K, Price TJ. Inhibition of carbonic anhydrase augments GABAA receptor-mediated analgesia via a spinal mechanism of action. J Pain. 2014 Apr;15(4):395–406.

10. Dickman A, Schneider J. The syringe driver: continuous subcutaneous infusions in palliative care. Fourth edition. Oxford: Oxford University Press; 2016.

11. Ainsworth SB, editor. Neonatal formulary: drug use in pregnancy and the first year of life. Eighth edition. Oxford: Oxford University Press, Incorporated; 2020.

12. Ziesenitz VC, Vaughns JD, Koch G, Mikus G, Van Den Anker JN. Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review. Clin Pharmacokinet. 2018 Feb;57(2):125–49.

13. King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. Palliat Med. 2011 Jul;25(5):525–52.

14. Antao B, Ooi K, Ade-Ajayi N, Stevens B, Spitz L. Effectiveness of alimemazine in controlling retching after Nissen fundoplication. J Pediatr Surg. 2005 Nov;40(11):1737–40.

15. De Bruyne P, Christiaens T, Boussery K, Mehuys E, Van Winckel M. Are antihistamines effective in children? A review of the evidence. Arch Dis Child. 2017 Jan;102(1):56–60.

16. Bramwell RG, Manford ML. Premedication of children with trimeprazine tartrate. Br J Anaesth. 1981 Aug;53(8):821–6.

17. Mitchell V, Grange C, Black A, Train J. A comparison of midazolam with trimeprazine as an oral premedicant for children. Anaesthesia. 1997 May;52(5):416–21.

18. Peters CG, Brunton JT. COMPARATIVE STUDY OF LORAZEPAM AND TRIMEPRAZINE FOR ORAL PREMEDICATION IN PAEDIATRIC ANAESTHESIA. Br J Anaesth. 1982 Jun;54(6):623–8.

19. Zorab JSM. Trimeprazine premedication in children. Anaesthesia. 1991 Dec;46(12):1088–1088.

20. France KG, Blampied NM, Wilkinson P. A multiple-baseline, double-blind evaluation of the effects of trimeprazine tartrate on infant sleep disturbance. Exp Clin Psychopharmacol. 1999 Nov;7(4):502–13.

21. Richman N. A double-blind drug trial of treatment in young children with waking problems. J Child Psychol Psychiatry. 1985 Jul;26(4):591–8.

22. Simonoff EA, Stores G. Controlled trial of trimeprazine tartrate for night waking. Arch Dis Child. 1987 Mar 1;62(3):253–7.

23. Loan WB, Cuthbert D. Adverse cardiovascular response to oral trimeprazine in children. BMJ. 1985 May 25;290(6481):1548–9.

24. Chambers FA, O'Leary E, Gormley PK, Flynn NM. Delayed profound respiratory depression after premedication with trimeprazine. Anaesthesia. 1992 Jul;47(7):585–6.

25. Mann NP. Trimeprazine and respiratory depression. Arch Dis Child. 1981 Jun;56(6):481–2.

26. Cooper TE, Heathcote LC, Clinch J, Gold JI, Howard R, Lord SM, et al. Antidepressants for chronic non-cancer pain in children and adolescents. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Aug 5 [cited 2023 May 17]; Available from: https://doi.wiley.com/10.1002/14651858.CD012535.pub2

27. Dharmshaktu P, Tayal V, Kalra BS. Efficacy of Antidepressants as Analgesics: A Review. J Clin Pharmacol. 2012 Jan;52(1):6–17.

28. Kaur R, Sinha VR. Antidepressants as antipruritic agents: A review. Eur Neuropsychopharmacol. 2018 Mar;28(3):341–52.

29. Niimi A, Chung KF. Evidence for neuropathic processes in chronic cough. Pulm Pharmacol Ther. 2015 Dec;35:100–4.

30. Watson CP. Therapeutic window for amitriptyline analgesia. Can Med Assoc J. 1984 Jan 15;130(2):105–6.

31. Patel B, Downie J, Bayliss J, Stephenson A, Bluebond-Langner M. Long-Term Daily Administration of Aprepitant for the Management of Intractable Nausea and Vomiting in Children With Life-Limiting Conditions: A Case Series. J Pain Symptom Manage. 2021 Sep;62(3):e225–31.

32. Patel P, Robinson PD, Thackray J, Flank J, Holdsworth MT, Gibson P, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update: PATEL ET AL . Pediatr Blood Cancer. 2017 Oct;64(10):e26542.

33. Gui S, Patel N, Issenman R, Kam AJ. Acute Management of Pediatric Cyclic Vomiting Syndrome: A Systematic Review. J Pediatr. 2019 Nov;214:158-164.e4.

34. Yang Y, Guo L, Chen Z, Jiang X, Liu Y. Benefits and harms of NK_1R antagonists in pruritus: A systematic review and meta-analysis. Dermatol Ther [Internet]. 2021 Jan [cited 2023 May 17];34(1). Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.14698

35. Cristofori F, Thapar N, Saliakellis E, Kumaraguru N, Elawad M, Kiparissi F, et al. Efficacy of the neurokinin-1 receptor antagonist aprepitant in children with cyclical vomiting syndrome. Aliment Pharmacol Ther. 2014 Aug;40(3):309–17.

36. He A, Alhariri JM, Sweren RJ, Kwatra MM, Kwatra SG. Aprepitant for the Treatment of Chronic Refractory Pruritus. BioMed Res Int. 2017;2017:1–6.

37. Andrews PLR, Golding JF, Sanger GJ. An assessment of the effects of neurokinin $_1$ receptor antagonism against nausea and vomiting: Relative efficacy, sites of action and lessons for future drug development. Br J Clin Pharmacol. 2023 Jul 15;bcp.15852.

38. Dias BLS, Fernandes AR, Maia Filho HDS. Sialorrhea in children with cerebral palsy. J Pediatr (Rio J). 2016 Nov;92(6):549–58.

39. You P, Strychowsky J, Gandhi K, Chen BA. Anticholinergic treatment for sialorrhea in children: A systematic review. Paediatr Child Health. 2021 May 17;27(2):82–7.

40. Azapağası E, Kendirli T, Perk O, Kutluk G, Öz Tunçer G, Teber S, et al. Sublingual Atropine Sulfate Use for Sialorrhea in Pediatric Patients. J Pediatr Intensive Care. 2020 Sep;09(03):196–200.

41. Michelon H, Larabi IA, Lemoine J, Alvarez J, Genevée A, Lillo-Lelouet A, et al. Atropine-induced toxicity after off-label sublingual administration of eyedrop for sialorrhoea treatment in neurological disabled patients. Br J Clin Pharmacol. 2021 Aug;87(8):3364–9.

42. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. Cochrane Database Syst Rev. 2008;(1):CD005177.

43. Rapoport A. Sublingual Atropine Drops for the Treatment of Pediatric Sialorrhea. J Pain Symptom Manage. 2010 Nov;40(5):783–8.

44. De Simone GG, Eisenchlas JH, Junin M, Pereyra F, Brizuela R. Atropine drops for drooling: a randomized controlled trial. Palliat Med. 2006 Oct;20(7):665–71.

45. Heisler M, Hamilton G, Abbott A, Chengalaram A, Koceja T, Gerkin R. Randomized double-blind trial of sublingual atropine vs. placebo for the management of death rattle. J Pain Symptom Manage. 2013 Jan;45(1):14–22.

46. Kintzel PE, Chase SL, Thomas W, Vancamp DM, Clements EA. Anticholinergic medications for managing noisy respirations in adult hospice patients. Am J Health Syst Pharm. 2009/02/24 ed. 2009 Mar 1;66(5):458–64.

47. Protus BM, Grauer PA, Kimbrel JM. Evaluation of Atropine 1% Ophthalmic Solution Administered Sublingually for the Management of Terminal Respiratory Secretions. Am J Hosp Palliat Med. 2013 Jun;30(4):388–92.

48. Shinjo T, Okada M. Atropine Eyedrops for Death Rattle in a Terminal Cancer Patient. J Palliat Med. 2013 Feb;16(2):212–3.

49. Yap R, Akhileswaran R, Heng CP, Tan A, Hui D. Comfort Care Kit: Use of Nonoral and Nonparenteral Rescue Medications at Home for Terminally Ill Patients with Swallowing Difficulty. J Palliat Med. 2014 May;17(5):575–8.

50. Wildiers H, Dhaenekint C, Demeulenaere P, Clement PMJ, Desmet M, Van Nuffelen R, et al. Atropine, Hyoscine Butylbromide, or Scopolamine Are Equally Effective for the Treatment of Death Rattle in Terminal Care. J Pain Symptom Manage. 2009 Jul;38(1):124–33.

51. Bird AM, Smith TL, Walton AE. Current treatment strategies for clozapine-induced sialorrhea. Ann Pharmacother. 2011 May;45(5):667–75.

52. Norderyd J, Graf J, Marcusson A, Nilsson K, Sjöstrand E, Steinwall G, et al. Sublingual administration of atropine eyedrops in children with excessive drooling-a pilot study. Int J Paediatr Dent. 2017 Jan;27(1):22–9.

53. Schwartz MD, Raulli R, Laney JW, Coley W, Walker R, O'Rourke AW, et al. Systemic Bioavailability of Sublingual Atropine Ophthalmic Solution: a Phase I Study in Healthy Volunteers with Implications for Use as a Contingency Medical Countermeasure. J Med Toxicol. 2022 Jul;18(3):187–97.

54. Remi C, Alrecht E. Subcutaneous use of baclofen. J Pain Symptom Manage. 2014;48(e1-3).

55. Hasnat MJ, Rice JE. Intrathecal baclofen for treating spasticity in children with cerebral palsy. Cochrane Movement Disorders Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Nov 13 [cited 2023 May 17];2015(11). Available from: http://doi.wiley.com/10.1002/14651858.CD004552.pub2

56. Adam E. A Systematic Review of the Effectiveness of Oral Baclofen in the Management of Hiccups in Adult Palliative Care Patients. J Pain Palliat Care Pharmacother. 2020 Jan 2;34(1):43–54.

57. Beecham E, Candy B, Howard R, McCulloch R, Laddie J, Rees H, et al. Pharmacological interventions for pain in children and adolescents with life-limiting conditions. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Mar 13 [cited 2023 May 17];2017(6). Available from: http://doi.wiley.com/10.1002/14651858.CD010750.pub2

58. Bohn E, Goren K, Switzer L, Falck-Ytter Y, Fehlings D. Pharmacological and neurosurgical interventions for individuals with cerebral palsy and dystonia: a systematic review update and meta-analysis. Dev Med Child Neurol. 2021 Sep;63(9):1038–50.

59. Moro C, Phelps C, Veer V, Clark J, Glasziou P, Tikkinen KAO, et al. The effectiveness of parasympathomimetics for treating underactive bladder: A systematic review and meta-analysis. Neurourol Urodyn. 2022 Jan;41(1):127–39.

60. Paul A, Punati J. What is the Evidence for Over the Counter Laxatives to Treat Childhood Constipation? Curr Gastroenterol Rep. 2021 Nov;23(11):19.

61. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. Eur J Drug Metab Pharmacokinet. 2019 Oct;44(5):591–609.

62. Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Gregoire MC, Ljungman G, et al. Opioids for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 19;7:CD012564.

63. Cooper TE, Fisher E, Gray AL, Krane E, Sethna N, van Tilburg MA, et al. Opioids for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 26;7:CD012538.

64. Lucenteforte E, Vagnoli L, Pugi A, Crescioli G, Lombardi N, Bonaiuti R, et al. A systematic review of the risk factors for clinical response to opioids for all-age patients with cancer-related pain and presentation of the paediatric STOP pain study. BMC Cancer. 2018/05/20 ed. 2018 May 18;18(1):568.

65. Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart JS. Buprenorphine for treating cancer pain. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Mar 31 [cited 2023 Jul 3];2018(12). Available from: http://doi.wiley.com/10.1002/14651858.CD009596.pub4

66. Noda J, Umeda S, Arai T, Harima A, Mori K. Continuous Subcutaneous Infusion of Buprenorphine for Cancer Pain Control: Clin J Pain. 1989 Jun;5(2):147–52.

67. Prommer E. Buprenorphine for Cancer Pain: Is It Ready for Prime Time? Am J Hosp Palliat Med. 2015 Dec;32(8):881–9.

68. Gralow I, Von Hornstein WF, Schleyer E, Hiddemann W. Kontinuierliche subkutane Buprenorphinapplikation in der Therapie karzinombedingter Schmerzen. Schmerz. 1995 May;9(3):117–23.

69. Kawamata T, Sato Y, Niiyama Y, Omote K, Namiki A. Pain management after lumbar spinal fusion surgery using continuous subcutaneous infusion of buprenorphine. J Anesth. 2005;19(3):199–203.

70. Greco R, Piastra M, Iacovacci V, Belcastro F, Forastiere EM, Proietti S, et al. [Continuous venous infusion of buprenorphine with autonomous elastomeric system in the control of postoperative pain]. Minerva Anestesiol. 1994 Oct;60(10 Suppl 2):1–8.

71. Kokki H, Rasanen I, Lasalmi M, Lehtola S, Ranta VP, Vanamo K, et al. Comparison of oxycodone pharmacokinetics after buccal and sublingual administration in children. Clin Pharmacokinet. 2006;45(7):745–54.

72. Kokki H, Rasanen I, Reinikainen M, Suhonen P, Vanamo K, Ojanpera I. Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. Clin Pharmacokinet. 2004;43(9):613–22.

73. Due MR, Yang XF, Allette YM, Randolph AL, Ripsch MS, Wilson SM, et al. Carbamazepine potentiates the effectiveness of morphine in a rodent model of neuropathic pain. PLoS One. 2014;9(9):e107399.

74. Ren Z, Yang B, Shi L, Sun QL, Sun AP, Lu L, et al. Carbamazepine Withdrawal-induced Hyperalgesia in Chronic Neuropathic Pain. Pain Physician. 2015 Nov;18(6):E1127-30.

75. Krishnaswami S, Hutmacher MM, Robbins JL, Bello A, West C, Bloom BJ. Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis. J Clin Pharmacol. 2012 Aug;52(8):1134–49.

76. Murto K, Lamontagne C, McFaul C, MacCormick J, Ramakko KA, Aglipay M, et al. Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study. Can J Anaesth. 2015 Jul;62(7):785–97.

77. Giordano T, Durkin A, Simi A, Shannon M, Dailey J, Facey H, et al. High-Dose Celecoxib for Pain After Pediatric Tonsillectomy: A Randomized Controlled Trial. Otolaryngol Neck Surg. 2023 Feb;168(2):218–26.

78. Faramarzi M, Roosta S, Eghbal MH, Nouri Rahmatabadi B, Faramarzi A, Mohammadi-Samani S, et al. Comparison of celecoxib and acetaminophen for pain relief in pediatric day case tonsillectomy: A randomized double-blind study. Laryngoscope Investig Otolaryngol. 2021 Dec;6(6):1307–15.

79. Drugs.com. Celecoxib: Usual pediatric dose for juvenile rheumatoid arthritis [Internet]. 2023. Available from: https://www.drugs.com/dosage/celecoxib.html

80. Joffe AR, Hogan J, Sheppard C, Tawfik G, Duff JP, Garcia Guerra G. Chloral hydrate enteral infusion for sedation in ventilated children: the CHOSEN pilot study. Crit Care. 2017 Nov 26;21(1):290.

81. Allen NM, Lin JP, Lynch T, King MD. Status dystonicus: a practice guide. Dev Med Child Neurol. 2013/12/07 ed. 2014 Feb;56(2):105–12.

82. MHRA Drug Safety Update. Chloral hydrate, cloral betaine (Welldorm): restriction of paediatric indication [Internet]. 2021. Available from: https://www.gov.uk/drug-safety-update/chloral-hydrate-cloral-betaine-welldorm-restriction-of-paediatric-indication

83. Fong CY, Lim WK, Li L, Lai NM. Chloral hydrate as a sedating agent for neurodiagnostic procedures in children. Cochrane Epilepsy Group, editor. Cochrane Database Syst Rev [Internet]. 2021 Aug 16 [cited 2023 May 20];2021(8). Available from: http://doi.wiley.com/10.1002/14651858.CD011786.pub3

84. Neonatal and Paediatric Pharmacists Group. Off label use of Chloral Hydrate in the Management of Intrusive Movement and Motor Disorders in Children and Young People [Internet]. 2021 [cited 2023 Sep 24]. Available from: https://nppg.org.uk/wp-content/uploads/2021/12/NPPG-Position-Statement-Chloral-Dystonia-V1.pdf

85. Saito J, Nadatani N, Setoguchi M, Nakao M, Kimura H, Sameshima M, et al. Potentially harmful excipients in neonatal medications: a multicenter nationwide observational study in Japan. J Pharm Health Care Sci. 2021 Dec;7(1):23.

86. Bascom PB, Bordley JL, Lawton AJ. High-dose neuroleptics and neuroleptic rotation for agitated delirium near the end of life. Am J Hosp Palliat Care. 2014 Dec;31(8):808–11.

87. Finucane AM, Jones L, Leurent B, Sampson EL, Stone P, Tookman A, et al. Drug therapy for delirium in terminally ill adults. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst

Rev [Internet]. 2020 Jan 21 [cited 2023 May 20]; Available from: https://doi.wiley.com/10.1002/14651858.CD004770.pub3

88. Kim SY, Simone S, Kishk OA, Graciano AL, Seung H, Edwards S. Chlorpromazine as Treatment for Refractory Agitation Associated with Pediatric Delirium. J Pediatr Pharmacol Ther. 2022 Dec 1;27(8):725–31.

89. Ahmed R, Maroney M, Fahim G, Ghin HL, Mathis AS. Evaluation of the use of chlorpromazine for agitation in pediatric patients. Ment Health Clin. 2021 Mar 1;11(2):40–4.

90. Chatha R, Huyton M, Hindley D, Clarke M. Using the 'benzodiazepine switch' in difficult childhood epilepsy. Dev Med Child Neurol. 2008 Aug;50(8):635–6.

91. Lwin EM, Ellis D, Song Y, Turner S, Garg S. Stability Studies of Extemporaneously Compounded Clobazam Oral Suspension. Ann Pharmacother. 2016 Feb;50(2):155–6.

92. Burns ML, Baftiu A, Opdal MS, Johannessen SI, Landmark CJ. Therapeutic Drug Monitoring of Clobazam and Its Metabolite-Impact of Age and Comedication on Pharmacokinetic Variability. Ther Drug Monit. 2016 Jun;38(3):350–7.

93. Gilmartin CGS, Dowd Z, Parker APJ, Harijan P. Interaction of cannabidiol with other antiseizure medications: A narrative review. Seizure. 2021 Mar;86:189–96.

94. Song L, Liu F, Liu Y, Zhang R, Ji H, Jia Y. Clonazepam add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020/04/21 ed. 2020 Apr 20;4(4):Cd012253.

95. Alvarenga-Brant R, Costa FO, Mattos-Pereira G, Esteves-Lima RP, Belém FV, Lai H, et al. Treatments for Burning Mouth Syndrome: A Network Meta-analysis. J Dent Res. 2023 Feb;102(2):135–45.

96. Schneider JJ, Good P, Ravenscroft PJ. Effect of tubing on loss of clonazepam administered by continuous subcutaneous infusion. J Pain Symptom Manage. 2006 Jun;31(6):563–7.

97. Zhu A, Benzon HA, Anderson TA. Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. Anesth Analg. 2017 Nov;125(5):1569–87.

98. Romantsik O, Calevo MG, Norman E, Bruschettini M. Clonidine for pain in non-ventilated infants. Cochrane Neonatal Group, editor. Cochrane Database Syst Rev [Internet]. 2020 Apr 9 [cited 2023 May 22];2020(4). Available from: http://doi.wiley.com/10.1002/14651858.CD013104.pub2

99. Wang Y, Guo Q, An Q, Zhao L, Wu M, Guo Z, et al. Clonidine as an Additive to Local Anesthetics in Caudal Block for Postoperative Analgesia in Pediatric Surgery: A Systematic Review and Meta-Analysis. Front Med. 2021 Sep 14;8:723191.

100. Eberl S, Ahne G, Toni I, Standing J, Neubert A. Safety of clonidine used for long-term sedation in paediatric intensive care: A systematic review. Br J Clin Pharmacol. 2021 Mar;87(3):785–805.

101. Howard P, Curtin J. Efficacy and safety of subcutaneous clonidine for refractory symptoms in palliative medicine: a retrospective study. BMJ Support Palliat Care [Internet]. 2022 Jun 30 [cited 2022 Jul 8]; Available from: https://spcare.bmj.com/content/early/2022/06/30/spcare-2022-003651

102. Hanning SM, Orlu Gul M, Toni I, Neubert A, Tuleu C. A mini-review of non-parenteral clonidine preparations for paediatric sedation. J Pharm Pharmacol. 2017 Mar 21;69(4):398–405.

103. Vasseur B, Dufour A, Houdas L, Goodwin H, Harries K, Emul NY, et al. Comparison of the Systemic and Local Pharmacokinetics of Clonidine Mucoadhesive Buccal Tablets with Reference Clonidine Oral Tablets in Healthy Volunteers: An Open-Label Randomised Cross-Over Trial. Adv Ther. 2017 Aug;34(8):2022–32.

104. Seger DL, Loden JK. Naloxone reversal of clonidine toxicity: dose, dose, dose. Clin Toxicol. 2018 Oct 3;56(10):873–9.

105. Giralt J, Tao Y, Kortmann RD, Zasadny X, Contreras-Martinez J, Ceruse P, et al. Randomized Phase 2 Trial of a Novel Clonidine Mucoadhesive Buccal Tablet for the Amelioration of Oral Mucositis in Patients Treated With Concomitant Chemoradiation Therapy for Head and Neck Cancer. Int J Radiat Oncol. 2020 Feb;106(2):320–8.

106. Gilkeson GS, Delaney RL. Effectiveness of Sublingual Clonidine in Patients Unable to Take Oral Medication. Drug Intell Clin Pharm. 1987 Mar;21(3):262–3.

107. McCluggage HL. Changing from continuous SC to transdermal clonidine to treat dystonia in a teenage boy with end-stage leucodystrophy. BMJ Support Palliat Care. 2018 Dec;8(4):433–5.

108. Bartz L, Klein C, Seifert A, Herget I, Ostgathe C, Stiel S. Subcutaneous Administration of Drugs in Palliative Care: Results of a Systematic Observational Study. J Pain Symptom Manage. 2014 Oct;48(4):540–7.

109. Nakou V, Williamson K, Arichi T, Lumsden DE, Tomlin S, Kaminska M, et al. Safety and efficacy of high-dose enteral, intravenous, and transdermal clonidine for the acute management of severe intractable childhood dystonia and status dystonicus: An illustrative case-series. Eur J Paediatr Neurol. 2017 Nov;21(6):823–32.

110. Woods S, Chandler E, Barton C. High Dose Clonidine as a Novel Therapy for Symptomatic Status Dystonicus in a Pediatric Patient (P5-9.009). In: Monday, April 24 [Internet]. Lippincott Williams & Wilkins; 2023 [cited 2023 Aug 2]. p. 2150. Available from: http://www.neurology.org/lookup/doi/10.1212/WNL.0000000000202348

111. Sayer C, Lumsden DE, Kaminska M, Lin JP. Clonidine use in the outpatient management of severe secondary dystonia. Eur J Paediatr Neurol. 2017 Jul;21(4):621–6.

112. MHRA Drug Safety Update. Codeine for analgesia: restricted use because of reports of morphine toxicity [Internet]. 2014 [cited 2023 May 22]. Available from: https://www.gov.uk/drug-safety-update/codeine-for-analgesia-restricted-use-in-children-because-of-reports-of-morphine-toxicity

113. Sutherland AE, Presland M, Harrop E, Carey M, Miller M, Wong ICKC. Orodispersible and transmucosal alternative medications for symptom control in adults. BMJ Support Palliat Care. 2022 Sep;12(3):305–15.

114. Masson R, Pagliano E, Baranello G. Efficacy of oral pharmacological treatments in dyskinetic cerebral palsy: a systematic review. Dev Med Child Neurol. 2017 Dec;59(12):1237–48.

115. Morse JD, Anderson BJ, Gastine S, Wong ICK, Standing JF. Pharmacokinetic modeling and simulation to understand diamorphine dose-response in neonates, children, and adolescents. Pediatr Anesth. 2022 Jun;32(6):716–26.

116. Abbas SQ. Diamorphine-Intrasite dressings for painful pressure ulcers. J Pain Symptom Manage. 2004 Dec;28(6):532–4.

117. Gastine S, Morse JD, Leung MT, Wong ICK, Howard RF, Harrop E, et al. Diamorphine pharmacokinetics and conversion factor estimates for intranasal diamorphine in paediatric breakthrough pain:systematic review. BMJ Support Palliat Care. 2022 Feb 19;bmjspcare-2021-003461.

118. McCoubrie R, Jeffrey. Intravesical Diamorphine for Bladder Spasm. J Pain Symptom Manage. 2003 Jan;25(1):1–3.

119. Friedrichsdorf S, Postier A. Management of breakthrough pain in children with cancer. J Pain Res. 2014 Mar;117.

120. Friedrichsdorf SJ. From Tramadol to Methadone: Opioids in the Treatment of Pain and Dyspnea in Pediatric Palliative Care. Clin J Pain. 2019 Jun;35(6):501–8.

121. Mathias NR, Hussain MA. Non-invasive Systemic Drug Delivery: Developability Considerations for Alternate Routes of Administration. J Pharm Sci. 2010 Jan;99(1):1–20.

122. McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Epilepsy Group, editor. Cochrane Database Syst Rev [Internet]. 2018 Jan 10 [cited 2023 May 23];2018(1). Available from: https://doi.wiley.com/10.1002/14651858.CD001905.pub3

123. Marel CD, Anderson BJ, Romsing J, Jacqz-Aigrain E, Tibboel D. Diclofenac and metabolite pharmacokinetics in children. Pediatr Anesth. 2004 Jun;14(6):443–51.

124. Standing JF, Tibboel D, Korpela R, Olkkola KT. Diclofenac pharmacokinetic meta-analysis and dose recommendations for surgical pain in children aged 1-12 years: Diclofenac pooled PK in children. Pediatr Anesth. 2011 Mar;21(3):316–24.

125. Standing JF, Howard RF, Johnson A, Savage I, Wong ICK. Population pharmacokinetics of oral diclofenac for acute pain in children. Br J Clin Pharmacol. 2008 Dec;66(6):846–53.

126. Ziesenitz VC, Welzel T, Van Dyk M, Saur P, Gorenflo M, Van Den Anker JN. Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years. Pediatr Drugs. 2022 Nov;24(6):603–55.

127. Guidelines on the management of chronic pain in children. Geneva: World Health Organization; 2020.

128. Junqueira DR, Bennett D, Huh SY, Fahrbach K, Neupane B, Betts M. Risk of Adverse Events Associated with Domperidone and Metoclopramide in Gastroparesis: Systematic Review and Meta-analysis. Drugs RD. 2023 Mar;23(1):1–20.

129. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. Br J Clin Pharmacol. 2005 Jun;59(6):725–9.

130. Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. Cochrane Database Syst Rev. 2014 Nov 24;(11):CD008550.

131. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. Br J Clin Pharmacol. 2015 Aug;80(2):200–8.

132. Corzo JL, Zambonino MA, Munoz C, Mayorga C, Requena G, Urda A, et al. Tolerance to COX-2 inhibitors in children with hypersensitivity to nonsteroidal anti-inflammatory drugs. Br J Dermatol. 2014 Mar;170(3):725–9.

133. Aanpreung P, Vanprapar N, Susiva C, Parkpreaw C, Boonyachart C. A randomized clinical trial comparing the efficacy of ranitidine and famotidine on intragastric acidity in critically ill pediatric patients. J Med Assoc Thail Chotmaihet Thangphaet. 1998 Mar;81(3):185–9.

134. Carroccio A, Pardo F, Montalto G, Iapichino L, Soresi M, Averna MR, et al. Use of famotidine in severe exocrine pancreatic insufficiency with persistent maldigestion on enzymatic replacement therapy. A long-term study in cystic fibrosis. Dig Dis Sci. 1992 Sep;37(9):1441–6.

135. James LP, Kearns GL. Pharmacokinetics and Pharmacodynamics of Famotidine in Paediatric Patients: Clin Pharmacokinet. 1996 Aug;31(2):103–10.

136. James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. J Clin Pharmacol. 1998 Dec;38(12):1089–95.

137. Maples HD, James LP, Stowe CD, Jones DP, Hak EB, Blumer JL, et al. Famotidine Disposition in Children and Adolescents with Chronic Renal Insufficiency. J Clin Pharmacol. 2003 Jan;43(1):7–14.

138. Miyake S, Yamada M, Iwamoto H, Yamashita S, Sugio Y. Effect of a new H2-blocker, famotidine, in reflux esophagitis among severely handicapped children. Clin Ther. 1987;9(5):548–58.

139. Nishimura M, Nakano S, Ueyama H, Uchiyama A, Tashiro C. Effect of preanesthetic rectal famotidine on pH and volume of gastric contents in pediatric outpatients. J Clin Anesth. 1991 May;3(3):207–10.

140. Orenstein SR, Shalaby TM, Devandry SN, Liacouras CA, Czinn SJ, Dice JE, et al. Famotidine for infant gastro-oesophageal reflux: a multi-centre, randomized, placebo-controlled, withdrawal trial. Aliment Pharmacol Ther. 2003 May 1;17(9):1097–107.

141. Oderda G, Dell'Olio D, Forni M, Farina L, Tavassoli K, Ansaldi N. Treatment of childhood peptic oesophagitis with famotidine or alginate-antacid. Ital J Gastroenterol. 1990 Dec;22(6):346–9.

142. Wenning LA, Murphy MG, James LP, Blumer JL, Marshall JD, Baier J, et al. Pharmacokinetics of Famotidine in Infants: Clin Pharmacokinet. 2005;44(4):395–406.

143. Madani S, Kauffman R, Simpson P, Lehr VT, Lai ML, Sarniak A, et al. Pharmacokinetics and pharmacodynamics of famotidine and ranitidine in critically ill children. J Clin Pharmacol. 2014 Feb;54(2):201–5.

144. Kraus GB, Braun GG, Götz H, Raithel S, Danner U. [Famotidine dosage in children. The effect of different doses on the pH and volume of the gastric juice]. Anaesthesist. 1990 Nov;39(11):587–92.

145. Treem WR, Davis PM, Hyams JS. Suppression of gastric acid secretion by intravenous administration of famotidine in children. J Pediatr. 1991 May;118(5):812–6.

146. Veevers AE, Oxberry SG. Ranitidine: forgotten drug of delayed gastric emptying. BMJ Support Palliat Care. 2017 Feb 3;bmjspcare-2016-001188.

147. Coombes L, Burke K, Anderson AK. The use of rapid onset fentanyl in children and young people for breakthrough cancer pain. Scand J Pain. 2017 Oct;17:256–9.

148. Lim SY, Woo S, Miller JL, Lewis TV, Henry ED, Johnson PN. Dosing for Fentanyl Infusion in Obese Children: Just Because It's What We Have Always Done Doesn't Mean It Is Right. J Pediatr Pharmacol Ther. 2018 May;23(3):223–6.

149. Pieper L, Wager J, Zernikow B. Intranasal fentanyl for respiratory distress in children and adolescents with life-limiting conditions. BMC Palliat Care. 2018 Sep 10;17(1):106.

150. Setlur A, Friedland H. Treatment of pain with intranasal fentanyl in pediatric patients in an acute care setting: a systematic review. Pain Manag. 2018 Sep 1;8(5):341–52.

151. McNair C, Graydon B, Taddio A. A cohort study of intranasal fentanyl for procedural pain management in neonates. Paediatr Child Health. 2018 Dec;23(8):e170–5.

152. Taylor N, Woods S, Hills M et al. Use of Buccal Fentanyl as a breakthrough opioid for symptom management in patients receiving palliative care. Arch Dis Child. 2023 Jul;108(Suppl 2):A33.

153. Pieper L, Zernikow B, Drake R, Frosch M, Printz M, Wager J. Dyspnea in Children with Life-Threatening and Life-Limiting Complex Chronic Conditions. J Palliat Med. 2018 Apr;21(4):552–64.

154. Zernikow B, Michel E, Anderson B. Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. J Pain. 2007 Mar;8(3):187–207.

155. Xiao Y, Yuan P, Sun Y, Xu Y, Deng X, Wang X, et al. Comparison of topical antifungal agents for oral candidiasis treatment: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Mar;133(3):282–91.

156. MHRA Drug Safety Update. SSRI/SNRI antidepressant medicines: small increased risk of postpartum haemorrhage when used in the month before delivery [Internet]. 2021 [cited 2023 May 24]. Available from: https://www.gov.uk/drug-safety-update/ssri-slash-snri-antidepressant-medicines-small-increased-risk-of-postpartum-haemorrhage-when-used-in-the-month-before-delivery

157. Liow NYK, Gimeno H, Lumsden DE, Marianczak J, Kaminska M, Tomlin S, et al. Gabapentin can significantly improve dystonia severity and quality of life in children. Eur J Paediatr Neurol. 2016 Jan;20(1):100–7.

158. Fehlings D, Brown L, Harvey A, Himmelmann K, Lin JP, Macintosh A, et al. Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review. Dev Med Child Neurol. 2018 Apr;60(4):356–66.

159. Egunsola O, Wylie CE, Chitty KM, Buckley NA. Systematic Review of the Efficacy and Safety of Gabapentin and Pregabalin for Pain in Children and Adolescents: Anesth Analg. 2019 Apr;128(4):811–9.

160. Siemens W, Xander C, Meerpohl JJ, Buroh S, Antes G, Schwarzer G, et al. Pharmacological interventions for pruritus in adult palliative care patients. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2016 Nov 16 [cited 2023 May 25];2016(11). Available from: http://doi.wiley.com/10.1002/14651858.CD008320.pub3

161. Cooper TE, Wiffen PJ, Heathcote LC, Clinch J, Howard R, Krane E, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Aug 5 [cited 2023 May 25]; Available from: https://doi.wiley.com/10.1002/14651858.CD012536.pub2

162. Safarpour Y, Vaziri ND, Jabbari B. Restless Legs Syndrome in Chronic Kidney Disease- a Systematic Review. Tremor Hyperkinetic Mov. 2023 Mar 29;13(1):10.

163. Mercadante S, Marinangeli F, Masedu F, Valenti M, Russo D, Ursini L, et al. Hyoscine Butylbromide for the Management of Death Rattle: Sooner Rather Than Later. J Pain Symptom Manage. 2018 Dec;56(6):902–7.

164. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Nov 2 [cited 2023 Jun 11];2020(10). Available from: http://doi.wiley.com/10.1002/14651858.CD006271.pub3

165. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth. 2016 Mar;63(3):311–25.

166. Li Y, Ma J, Lu G, Dou Z, Knaggs R, Xia J, et al. Hydromorphone for cancer pain. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2021 Aug 5 [cited 2023 Jun 1];2021(8). Available from: http://doi.wiley.com/10.1002/14651858.CD011108.pub3

167. Spénard S, Gélinas C, D. Trottier E, Tremblay-Racine F, Kleiber N. Morphine or hydromorphone: which should be preferred? A systematic review. Arch Dis Child. 2021 Oct;106(10):1002–9.

168. MRHA. Hyoscine butylbromide (Buscopan) injection: risk of serious adverse effects in patients with underlying cardiac disease [Internet]. GOV.UK; 2017. Available from: https://www.gov.uk/drug-safety-update/hyoscine-butylbromide-buscopan-injection-risk-of-serious-adverse-effects-in-patients-with-underlying-cardiac-disease

169. Van Esch HJ, Van Zuylen L, Geijteman ECT, Oomen-de Hoop E, Huisman BAA, Noordzij-Nooteboom HS, et al. Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life: The SILENCE Randomized Clinical Trial. JAMA. 2021 Oct 5;326(13):1268.

170. Taburee W, Dhippayom T, Nagaviroj K, Dilokthornsakul P. Effects of Anticholinergics on Death Rattle: A Systematic Review and Network Meta-Analysis. J Palliat Med. 2023 Mar 1;26(3):431–40.

171. NICE Clinical Guideline. NG62 Cerebral palsy in under 25s: assessment and management [Internet]. 2017 [cited 2023 Jul 31]. Available from: https://www.nice.org.uk/guidance/ng62/resources/cerebral-palsy-in-under-25s-assessment-and-management-pdf-1837570402501

172. Wong T, Stang AS, Ganshorn H, Hartling L, Maconochie IK, Thomsen AM, et al. Combined and alternating paracetamol and ibuprofen therapy for febrile children. Cochrane Infectious Diseases Group, editor. Cochrane Database Syst Rev [Internet]. 2013 Oct 30 [cited 2023 Jun 2]; Available from: https://doi.wiley.com/10.1002/14651858.CD009572.pub2

173. Tan E, Braithwaite I, McKinlay CJD, Dalziel SR. Comparison of Acetaminophen (Paracetamol) With Ibuprofen for Treatment of Fever or Pain in Children Younger Than 2 Years: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Oct 30;3(10):e2022398.

174. Sherbash M, Furuya-Kanamori L, Nader JD, Thalib L. Risk of wheezing and asthma exacerbation in children treated with paracetamol versus ibuprofen: a systematic review and meta-analysis of randomised controlled trials. BMC Pulm Med. 2020 Dec;20(1):72.

175. Okpapi A, Friend AJ, Turner SW. Asthma and other recurrent wheezing disorders in children (acute). BMJ Clin Evid. 2012 Jul 6;2012:0300.

176. Santos Junior LC, Santos JR, Reis A, Faria-e-Silva AL, Leal PC. Effectiveness of the pharmacological treatments for sialorrhea in patients with Parkinson's disease: a systematic review and network meta-analysis. Clin Oral Investig [Internet]. 2023 Apr 10 [cited 2023 Jun 2]; Available from: https://link.springer.com/10.1007/s00784-023-04981-9

177. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol. 2014 Feb;77(2):357–67.

178. Taylor M, Jakacki R, May C, Howrie D, Maurer S. Ketamine PCA for treatment of end-of-life neuropathic pain in pediatrics. Am J Hosp Palliat Care. 2015 Dec;32(8):841–8.

179. Majidi S, Parna A, Zamani M, Akhbari K. Onset and Effect Duration of Intrabuccal Space and Intramuscular Ketamine in Pediatrics. Adv Biomed Res. 2018;7:91.

180. Cheung HM, Yew DTW. Effects of Perinatal Exposure to Ketamine on the Developing Brain. Front Neurosci. 2019 Feb 22;13:138.

181. Benini F, Congedi S, Giacomelli L, Papa S, Shah A, Milani G. Refractory symptoms in paediatric palliative care: can ketamine help? Drugs Context. 2021 May 19;10:1–9.

182. Mercadante S, Caruselli A, Casuccio A. The use of ketamine in a palliative-supportive care unit: a retrospective analysis. Ann Palliat Med. 2018 Apr;7(2):205–10.

183. Rosati A, De Masi S, Guerrini R. Ketamine for Refractory Status Epilepticus: A Systematic Review. CNS Drugs. 2018 Nov;32(11):997–1009.

184. Bredlau AL, McDermott MP, Adams HR, Dworkin RH, Venuto C, Fisher SG, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. J Pediatr. 2013 Jul;163(1):194-200 e1.

185. Gillis JC, Brogden RN. Ketorolac. A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs. 1997 Jan;53(1):139–88.

186. Cozzi G, Zanchi C, Chiaretti A, Tipo V, Cernich M, D'Anna C, et al. Administering analgesia sublingually is a suitable option for children with acute abdominal pain in the emergency department. Acta Paediatr. 2019 Jan;108(1):143–8.

187. Neri E, Maestro A, Minen F, Montico M, Ronfani L, Zanon D, et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. Arch Dis Child. 2013 Sep 1;98(9):721–4.

188. McNicol ED, Rowe E, Cooper TE. Ketorolac for postoperative pain in children. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2018 Jul 7 [cited 2023 Jun 2]; Available from: https://doi.wiley.com/10.1002/14651858.CD012294.pub2

189. Vacha ME, Huang W, Mando-Vandrick J. The Role of Subcutaneous Ketorolac for Pain Management. Hosp Pharm. 2015 Feb;50(2):108–12.

190. Southwell BR. Treatment of childhood constipation: a synthesis of systematic reviews and meta-analyses. Expert Rev Gastroenterol Hepatol. 2020 Mar 3;14(3):163–74.

191. Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy. Am J Gastroenterol. 2013 Sep;108(9):1458–63.

192. Qiao MY, Cui HT, Zhao LZ, Miao JK, Chen QX. Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures: A Systematic Review and Meta-Analysis. Front Neurol. 2021 Nov 18;12:747745.

193. Hooper RG, Ramaswamy VV, Wahid RM, Satodia P, Bhulani A. Levetiracetam as the first-line treatment for neonatal seizures: a systematic review and meta-analysis. Dev Med Child Neurol. 2021 Nov;63(11):1283–93.

194. Dalziel SR, Furyk J, Bonisch M, Oakley E, Borland M, Neutze J, et al. A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT)-a PREDICT study. BMC Pediatr. 2017 Jun 22;17(1):152.

195. Kim HJ, Kim SH, Kang HC, Lee JS, Chung HJ, Kim HD. Adjunctive levetiracetam treatment in pediatric Lennox-Gastaut syndrome. Pediatr Neurol. 2014 Oct;51(4):527–31.

196. Kim JS, Lee JH, Ryu HW, Lim BC, Hwang H, Chae JH, et al. Effectiveness of intravenous levetiracetam as an adjunctive treatment in pediatric refractory status epilepticus. Pediatr Emerg Care. 2014 Aug;30(8):525–8.

197. Li Z ran, Wang C yu, Zhu X, Jiao Z. Population Pharmacokinetics of Levetiracetam: A Systematic Review. Clin Pharmacokinet. 2021 Mar;60(3):305–18.

198. Nevitt SJ, Sudell M, Cividini S, Marson AG, Tudur Smith C. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Epilepsy Group, editor. Cochrane Database Syst Rev [Internet]. 2022 Apr 1 [cited 2023 Jun 4];2022(4). Available from: http://doi.wiley.com/10.1002/14651858.CD011412.pub4

199. Resuscitation Council UK. Algorithm for management of convulsive status epilepticus in children. 2021.

200. Hohl CM, Stenekes S, Harlos MS, Shepherd E, McClement S, Chochinov HM. Methotrimeprazine for the management of end-of-life symptoms in infants and children. J Palliat Care. 2014/01/02 ed. 2013 Autumn;29(3):178–85.

201. Dietz I, Schmitz A, Lampey I, Schulz C. Evidence for the use of Levomepromazine for symptom control in the palliative care setting: a systematic review. BMC Palliat Care. 2013 Jan 19;12:2.

202. Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2013 Aug 29 [cited 2023 Jun 4]; Available from: https://doi.wiley.com/10.1002/14651858.CD004844.pub3

203. Cox L, Darvill E, Dorman S. Levomepromazine for nausea and vomiting in palliative care. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2015 Nov 2 [cited 2023 Jun 4];2017(5). Available from: http://doi.wiley.com/10.1002/14651858.CD009420.pub3

204. Sommer C, Cruccu G. Topical Treatment of Peripheral Neuropathic Pain: Applying the Evidence. J Pain Symptom Manage. 2017 Mar;53(3):614–29.

205. Nalamachu S, Wieman M, Bednarek L, Chitra S. Influence of anatomic location of lidocaine patch 5% on effectiveness and tolerability for postherpetic neuralgia. Patient Prefer Adherence. 2013;7:551–7.

206. Goddard JM, Reaney RL. Lidocaine 5%-medicated plaster (Versatis) for localised neuropathic pain: results of a multicentre evaluation of use in children and adolescents. Br J Pain. 2018/07/31 ed. 2018 Aug;12(3):189–93.

207. Florez ID, Veroniki AA, Al Khalifah R, Yepes-Nuñez JJ, Sierra JM, Vernooij RWM, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: A systematic review and network meta-analysis. Van Wouwe JP, editor. PLOS ONE. 2018 Dec 5;13(12):e0207701.

208. Vande Velde S, Van Renterghem K, Van Winkel M, De Bruyne R, Van Biervliet S. Constipation and fecal incontinence in children with cerebral palsy. Overview of literature and flowchart for a stepwise approach. Acta Gastro-Enterol Belg. 2018;81(3):415–8.

209. Omar MI, Alexander CE. Drug treatment for faecal incontinence in adults. Cochrane Incontinence Group, editor. Cochrane Database Syst Rev [Internet]. 2013 Jun 11 [cited 2023 Jun 4]; Available from: https://doi.wiley.com/10.1002/14651858.CD002116.pub2

210. Zhao Z yu, Wang H ying, Wen B, Yang Z bo, Feng K, Fan J chun. A Comparison of Midazolam, Lorazepam, and Diazepam for the Treatment of Status Epilepticus in Children: A Network Meta-analysis. J Child Neurol. 2016 Aug;31(9):1093–107.

211. Chhabra R, Gupta R, Gupta LK. Intranasal midazolam versus intravenous/rectal benzodiazepines for acute seizure control in children: A systematic review and meta-analysis. Epilepsy Behav. 2021 Dec;125:108390.

212. Kong W, Deng H, Wan J, Zhou Y, Zhou Y, Song B, et al. Comparative Remission Rates and Tolerability of Drugs for Generalised Anxiety Disorder: A Systematic Review and Network Meta-analysis of Double-Blind Randomized Controlled Trials. Front Pharmacol. 2020 Nov 11;11:580858.

213. Li Y, Ma J, Jin Y, Li N, Zheng R, Mu W, et al. Benzodiazepines for treatment of patients with delirium excluding those who are cared for in an intensive care unit. Cochrane Dementia and Cognitive Improvement Group, editor. Cochrane Database Syst Rev [Internet]. 2020 Feb 28 [cited 2023 Jun 4];2020(2). Available from: http://doi.wiley.com/10.1002/14651858.CD012670.pub2

214. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus Polyethylene Glycol for Chronic Constipation. Cochrane Database Syst Rev. 2010;(7):CD007570.

215. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane IBD Group, editor. Cochrane Database Syst Rev [Internet]. 2016 Aug 17 [cited 2023 Jun 4];2018(8). Available from: http://doi.wiley.com/10.1002/14651858.CD009118.pub3

216. De Giorgio R, Zucco FM, Chiarioni G, Mercadante S, Corazziari ES, Caraceni A, et al. Management of Opioid-Induced Constipation and Bowel Dysfunction: Expert Opinion of an Italian Multidisciplinary Panel. Adv Ther. 2021 Jul;38(7):3589–621.

217. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8(5):e63773.

218. Esposito S, Laino D, D'Alonzo R, Mencarelli A, Di Genova L, Fattorusso A, et al. Pediatric sleep disturbances and treatment with melatonin. J Transl Med. 2019 Dec;17(1):77.

219. Choi K, Lee YJ, Park S, Je NK, Suh HS. Efficacy of melatonin for chronic insomnia: Systematic reviews and meta-analyses. Sleep Med Rev. 2022 Dec;66:101692.

220. Parker A, Beresford B, Dawson V, Elphick H, Fairhurst C, Hewitt C, et al. Oral melatonin for non-respiratory sleep disturbance in children with neurodisabilities: systematic review and meta-analyses. Dev Med Child Neurol. 2019 Aug;61(8):880–90.

221. Beresford B, McDaid C, Parker A, Scantlebury A, Spiers G, Fairhurst C, et al. Pharmacological and non-pharmacological interventions for non-respiratory sleep disturbance in children with neurodisabilities: a systematic review. Health Technol Assess. 2018 Oct;22(60):1–296.

222. Madden K, Jo E, Williams JL, Liu D, Bruera E. Corrected QT Interval Prolongation in Pediatric and Young Adult Patients on Methadone for Cancer-Related Pain. J Pain Symptom Manage. 2019 Oct;58(4):678–84.

223. WHO. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. 2012.

224. McLean S, Twomey F. Methods of Rotation From Another Strong Opioid to Methadone for the Management of Cancer Pain: A Systematic Review of the Available Evidence. J Pain Symptom Manage. 2015 Aug;50(2):248-259.e1.

225. Benedetti F, Zoletto S, Salerno A, Avagnina I, Benini F. Old Drug, New Pain. Roles and Challenges of Methadone Therapy in Pediatric Palliative Care: A Systematic Review. Front Pediatr. 2022 May 27;10:874529.

226. Liu J, Smith KE, Riker RR, Craig WY, McKelvy DJ, Kemp HD, et al. Methadone bioavailability and dose conversion implications with intravenous and enteral administration: A scoping review. Am J Health Syst Pharm. 2021 Jul 22;78(15):1395–401.

227. Madden K, Park M, Liu D, Bruera E. The frequency of QTc prolongation among pediatric and young adult patients receiving methadone for cancer pain. Pediatr Blood Cancer [Internet]. 2017 Nov;64(11). Available from: https://www.ncbi.nlm.nih.gov/pubmed/28449209

228. Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Feb 8 [cited 2023 Jun 10];2017(3). Available from: http://doi.wiley.com/10.1002/14651858.CD003971.pub4

229. Heppe DB, Haigney MC, Krantz MJ. The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study. J Palliat Med. 2010/07/06 ed. Jun;13(6):638–9.

230. Habashy C, Springer E, Hall EA, Anghelescu DL. Methadone for Pain Management in Children with Cancer. Paediatr Drugs. 2018 Oct;20(5):409–16.

231. Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med. 2015 Mar;175(3):420–7.

232. Fife A, Postier A, Flood A, Friedrichsdorf SJ. Methadone conversion in infants and children: Retrospective cohort study of 199 pediatric inpatients. J Opioid Manag. 2016 May;12(2):123–30.

233. Hall EA, Sauer HE, Habashy C, Anghelescu DL. Methadone for Cancer Pain in Pediatric End-of-Life Care. Am J Hosp Palliat Med. 2021 Aug;38(8):914–9.

234. Flerlage JE, Baker JN. Methylnaltrexone for Opioid-Induced Constipation in Children and Adolescents and Young Adults with Progressive Incurable Cancer at the End of Life. J Palliat Med. 2015 Jul;18(7):631–3.

235. Diego L, Atayee R, Helmons P, von Gunten CF. Methylnaltrexone: a novel approach for the management of opioid-induced constipation in patients with advanced illness. Expert Rev Gastroenterol Hepatol. 2009 Oct;3(5):473–85.

236. Candy B, Jones L, Vickerstaff V, Larkin PJ, Stone P. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2018 Jun 5 [cited 2023 Jun 10];2018(6). Available from: http://doi.wiley.com/10.1002/14651858.CD006332.pub3

237. Rauck RL, Slatkin NE, Stambler N, Israel RJ. Safety of oral methylnaltrexone for opioid-induced constipation in patients with chronic noncancer pain. J Pain Res. 2018 Dec;Volume 12:139–50.

238. Davis M, Hui D, Davies A, Ripamonti C, Capela A, DeFeo G, et al. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2021 Dec;29(12):8089–96.

239. Lau Moon Lin M, Robinson PD, Flank J, Sung L, Dupuis LL. The Safety of Metoclopramide in Children: A Systematic Review and Meta-Analysis. Drug Saf. 2016 Jul;39(7):675–87.

240. Jeon YS, Kearney AM, Baker PG. Management of hiccups in palliative care patients. BMJ Support Palliat Care. 2018 Mar;8(1):1–6.

241. Castro V de. Odor management in fungating wounds with metronidazole: a systematic review. JHPN. 2015;17(1):73–9.

242. O'Neill L, Nelson Z, Ahmad N, Fisher AH, Denton A, Renzi M, et al. Malignant Fungating Wounds of the Head and Neck: Management and Antibiotic Stewardship. OTO Open [Internet]. 2022 Jan [cited 2023 May 25];6(1). Available from: https://onlinelibrary.wiley.com/doi/10.1177/2473974X211073306

243. Pacifici GM. Clinical Pharmacology of Midazolam in Neonates and Children: Effect of Disease—A Review. Int J Pediatr. 2014;2014:1–20.

244. Altamimi MI, Sammons H, Choonara I. Inter-individual variation in midazolam clearance in children. Arch Dis Child. 2015 Jan;100(1):95–100.

245. Flores-Pérez C, Flores-Pérez J, Moreno-Rocha LA, Chávez-Pacheco JL, Noguez-Méndez NA, Ramírez-Mendiola B, et al. Influence of Age and Sex on the Pharmacokinetics of Midazolam and the Depth of Sedation in Pediatric Patients Undergoing Minor Surgeries. Pharmaceutics. 2023 Jan 29;15(2):440.

246. Bouw MR, Chung SS, Gidal B, King A, Tomasovic J, Wheless JW, et al. Clinical pharmacokinetic and pharmacodynamic profile of midazolam nasal spray. Epilepsy Res. 2021 Mar;171:106567.

247. Kienitz R, Kay L, Beuchat I, Gelhard S, Von Brauchitsch S, Mann C, et al. Benzodiazepines in the Management of Seizures and Status Epilepticus: A Review of Routes of Delivery, Pharmacokinetics, Efficacy, and Tolerability. CNS Drugs. 2022 Sep;36(9):951–75.

248. Midazolam: Summary of Product Characteristics [Internet]. Electronic Medicines Compendium. [cited 2023 Jun 25]. Available from: https://www.medicines.org.uk/emc/product/7460/smpc

249. Stuart-harris R, Joel SP, McDonald P, Currow D, Slevin ML. The pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus injection and subcutaneous infusion of morphine: *Pharmacokinetics of subcutaneous morphine*. Br J Clin Pharmacol. 2000 Mar;49(3):207–14.

250. Polito S, MacDonald T, Romanick M, Jupp J, Wiernikowski J, Vennettilli A, et al. Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: A multicenter, retrospective review. Pediatr Blood Cancer. 2018 Dec;65(12):e27374.

251. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, Oñate-Ocaña LF, Zatarain-Barrón ZL, Barrón F, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. Support Care Cancer. 2018 Sep;26(9):3029–38.

252. Clarke SFJ. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J. 2005 Sep 1;22(9):612–6.

253. Clarke S, Dargan P. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Intravenous or intramuscular/subcutaneous naloxone in opioid overdose. Emerg Med J EMJ. 2002 May;19(3):249.

254. Wanger K, Brough L, Macmillan I, Goulding J, MacPhail I, Christenson JM. Intravenous vs Subcutaneous Naloxone for Out-of-hospital Management of Presumed Opioid Overdose. Acad Emerg Med. 1998 Apr;5(4):293–9.

255. Dettmer K. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. BMJ. 2001 Apr 14;322(7291):895–6.

256. McDonald R, Lorch U, Woodward J, Bosse B, Dooner H, Mundin G, et al. Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study: Concentrated naloxone nasal spray pharmacokinetics. Addiction. 2018 Mar;113(3):484–93.

257. Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Dale O. Naloksonnesespray-biotilgjengelighet og opptaksmønster i en fase 1-studie. Tidsskr Den Nor Legeforening [Internet]. 2019 [cited 2023 Jul 8]; Available from: https://tidsskriftet.no/2019/09/originalartikkel/naloksonnesespray-biotilgjengelighet-og-opptaksmonster-i-en-fase-1-studie

258. Malmros Olsson E, Lönnqvist P, Stiller C, Eksborg S, Lundeberg S. Rapid systemic uptake of naloxone after intranasal administration in children. Pediatr Anesth. 2021 Jun;31(6):631–6.

259. Heinrich M, Menzel C, Hoffmann F, Berger M, Schweinitz D. Self-administered procedural analgesia using nitrous oxide/oxygen (50:50) in the pediatric surgery emergency room: effectiveness and limitations. Eur J Pediatr Surg. 2015 Jun;25(3):250–6.

260. Ingelmo P, Wei A, Rivera G. Nitrous oxide for procedural analgesia at home in a child with epidermolysis bullosa. Paediatr Anaesth. 2017 Jul;27(7):776–8.

261. Young A, Ismail M, Papatsoris AG, Barua JM, Calleary JG, Masood J. Entonox® inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. Ann R Coll Surg Engl. 2012 Jan;94(1):8–11.

262. Hao W, Piao L, Sun M, Zeng F. Clinical effect of combination of octreotide and omeprazole in children with acute upper gastrointestinal bleeding and the levels of serum creatinine and serum urea nitrogen. Pak J Pharm Sci. 2022 Jan;35(1(Special)):343–7.

263. Jenkinson AC, McGuinness J, Prendiville T. Octreotide for Acquired Chylothorax in Pediatric Patients Post-Cardiothoracic Surgery for Congenital Heart Disease: A Systematic Review. Pediatr Cardiol. 2023 Feb;44(2):297–305.

264. Mas E, Borrelli O, Broekaert I, de-Carpi JM, Dolinsek J, Miele E, et al. Drugs in Focus: Octreotide Use in Children With Gastrointestinal Disorders. J Pediatr Gastroenterol Nutr. 2022 Jan;74(1):1–6.

265. Bellini C, Cabano R, De Angelis LC, Bellini T, Calevo MG, Gandullia P, et al. Octreotide for congenital and acquired chylothorax in newborns: A systematic review: Octreotide and neonatal chylothorax. J Paediatr Child Health. 2018 Aug;54(8):840–7.

266. Peled O, Lavan O, Stein J, Vinograd I, Yahel A, Valevski A, et al. Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer. J Child Adolesc Psychopharmacol. 2020 Oct 1;30(8):486–94.

267. Saudemont G, Prod'Homme C, Da Silva A, Villet S, Reich M, Penel N, et al. The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. BMC Palliat Care. 2020 Dec;19(1):56.

268. Agar M, Webster R, Lacey J, Donovan B, Walker A. The use of subcutaneous omeprazole in the treatment of dyspepsia in palliative care patients. J Pain Symptom Manage. 2004 Dec;28(6):529–31.

269. Niño-Serna LF, Acosta-Reyes J, Veroniki AA, Florez ID. Antiemetics in Children With Acute Gastroenteritis: A Meta-analysis. Pediatrics. 2020 Apr 1;145(4):e20193260.

270. Patel P, Robinson PD, Wahib N, Cheung P, Wong T, Cabral S, et al. Interventions for the prevention of acute phase chemotherapy-induced nausea and vomiting in adult and pediatric patients: a systematic review and meta-analysis. Support Care Cancer. 2022 Nov;30(11):8855–69.

271. Porcel JM, Salud A, Porta J, Schoenenberger JA. Antiemetic efficacy of subcutaneous 5-HT3 receptor antagonists in terminal cancer patients. J Pain Symptom Manage. 1998 May;15(5):265–6.

272. Mulvenna PaulaM, Regnard ClaudFB. Subcutaneous ondansetron. The Lancet. 1992 Apr;339(8800):1059.

273. Palliative Physician Lead, Windsor Regional Hospital, Clinical Lead, Palliative Care, Hôtel-Dieu Grace Health Care, 1453 Prince Rd, Windsor, ON N9C 3Z4, Canada, Aoun L, Zakaria J, Palliative Physician Lead, Windsor Regional Hospital, Clinical Lead, Palliative Care, Hôtel-Dieu Grace Health Care, 1453 Prince Rd, Windsor, ON N9C 3Z4, Canada. A Case Report of Continuous Subcutaneous Infusion of Hydromorphone, Metoclopramide and Ondansetron Used To Treat Refractory Pain and Nausea in an Ambulatory Palliative Clinic. Palliat Med Hosp Care-Open J. 2017 Jun 28;3(1):1–4.

274. Sevinc AH. A prospective and randomised trial of efficacy and safety of transdermal oxybutynin (TOP) versus oral oxybutynin in the management of children with overactive bladder. Eur Urol Open Sci. 2020;19(Supplement 2)(Conference: EAU20 Virtual Congress and Theme Week. Virtual, Online.).

275. Cohn JA, Brown ET, Reynolds WS, Kaufman MR, Milam DF, Dmochowski RR. An update on the use of transdermal oxybutynin in the management of overactive bladder disorder. Ther Adv Urol. 2016 Apr;8(2):83–90.

276. Vozmediano-Chicharro R, Blasco Hernández P, Madurga-Patuel B. Insights into the Management of Overactive Bladder with Transdermal Oxybutynin: A Practical Review. Res Rep Urol. 2020 Aug;Volume 12:321–30.

277. Shen S hong, Jia X, Peng L, Zeng X, Shen H, Luo D yi. Intravesical oxybutynin therapy for patients with neurogenic detrusor overactivity: a systematic review and meta-analysis. Int Urol Nephrol. 2022 Apr;54(4):737–47.

278. Guerra LA, Moher D, Sampson M, Barrowman N, Pike J, Leonard M. Intravesical Oxybutynin for Children With Poorly Compliant Neurogenic Bladder: A Systematic Review. J Urol. 2008 Sep;180(3):1091–7.

279. Haferkamp A, Staehler G, Gerner H, Dörsam J. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. Spinal Cord. 2000 Apr;38(4):250–4.

280. Buyse G, Waldeck K, Verpoorten C, Bjork H, Casaer P, Andersson KE. INTRAVESICAL OXYBUTYNIN FOR NEUROGENIC BLADDER DYSFUNCTION: LESS SYSTEMIC SIDE EFFECTS DUE TO REDUCED FIRST PASS METABOLISM. J Urol. 1998 Sep;160(3 Part 1):892–6.

281. Ferrara P, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E. Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida: SIDE-EFFECTS OF ORAL OR INTRAVESICAL OXYBUTYNIN IN SPINA BIFIDA. BJU Int. 2001 May;87(7):674–8.

282. Amark, Eksborg, Juneskans, Bussman, Palm. Pharmacokinetics and effects of intravesical oxybutynin on the paediatric neurogenic bladder. BJU Int. 1998 Dec;82(6):859–64.

283. Painter KA, Vates TS, Bukowski TP, Fleming P, Freedman AL, Smith CA, et al. Long-term intravesical oxybutynin chloride therapy in children with myelodysplasia. J Urol. 1996 Oct;156(4):1459–62.

284. Malik MF, Randall JH, Campbell JG, McLaughlin MJ, Koenig JF. Dosing Variability and Clinical Outcomes of Oxybutynin: A Pediatric Cohort of Patients With Neurogenic Bladder. Top Spinal Cord Inj Rehabil. 2022 Jun 1;28(3):9–14.

285. Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS, Page AJ, et al. Oxycodone for cancer-related pain. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2022 Jun 9 [cited 2023 May 27];2022(6). Available from: http://doi.wiley.com/10.1002/14651858.CD003870.pub7

286. Kokki H, Lintula H, Vanamo K, Heiskanen M, Eskelinen M. Oxycodone vs Placebo in Children With Undifferentiated Abdominal Pain: A Randomized, Double-blind Clinical Trial of the Effect of Analgesia on Diagnostic Accuracy. Arch Pediatr Adolesc Med. 2005 Apr 1;159(4):320.

287. Kinnunen M, Piirainen P, Kokki H, Lammi P, Kokki M. Updated Clinical Pharmacokinetics and Pharmacodynamics of Oxycodone. Clin Pharmacokinet. 2019 Jun;58(6):705–25.

288. Kochovska S, Ferreira DH, Garcia MV, Phillips JL, Currow DC. Perspectives on palliative oxygen for breathlessness: systematic review and meta-synthesis. Eur Respir J. 2021 Oct;58(4):2004613.

289. Hasegawa T, Ochi T, Goya S, Matsuda Y, Kako J, Watanabe H, et al. Efficacy of supplemental oxygen for dyspnea relief in patients with advanced progressive illness: A systematic review and meta-analysis. Respir Investig. 2023 Jul;61(4):418–37.

290. Wilson ME, Mittal A, Dobler CC, Curtis JR, Majzoub AM, Soleimani J, et al. High-Flow Nasal Cannula Oxygen in Patients with Acute Respiratory Failure and Do-Not-Intubate or Do-Not-Resuscitate Orders: A Systematic Review. J Hosp Med. 2020 Feb;15(2):101–6.

291. Swan F, Newey A, Bland M, Allgar V, Booth S, Bausewein C, et al. Airflow relieves chronic breathlessness in people with advanced disease: An exploratory systematic review and meta-analyses. Palliat Med. 2019 Jun;33(6):618–33.

292. Celin MR, Simon JC, Krzak JJ, Fial AV, Kruger KM, Smith PA, et al. Do Bisphosphonates Alleviate Pain in Children? A Systematic Review. Curr Osteoporos Rep. 2020 Oct;18(5):486–504.

293. Constantino CS, Krzak JJ, Fial AV, Kruger KM, Rammer JR, Radmanovic K, et al. Effect of Bisphosphonates on Function and Mobility Among Children With Osteogenesis Imperfecta: A Systematic Review. JBMR Plus. 2019 Oct;3(10):e10216.

294. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Cystic Fibrosis and Genetic Disorders Group, editor. Cochrane Database Syst Rev [Internet]. 2016 Oct 19 [cited 2023 Jun 24];2016(10). Available from: http://doi.wiley.com/10.1002/14651858.CD005088.pub4

295. Giri D, Ramakrishnan R, Hayden J, Brook L, Das U, Mughal MZ, et al. Denosumab Therapy for Refractory Hypercalcemia Secondary to Squamous Cell Carcinoma of Skin in Epidermolysis Bullosa. World J Oncol. 2015 Apr;6(2):345–8.

296. NICE guidline. NG 143: Fever in under 5s: assessment and initial management [Internet]. 2019 [cited 2023 May 28]. Available from: https://www.nice.org.uk/guidance/ng143

297. Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 2;8:CD012539.

298. Cooper TE, Heathcote LC, Anderson B, Grégoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. Cochrane Pain, Palliative and Supportive Care Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Jul 24 [cited 2023 May 28];2019(10). Available from: http://doi.wiley.com/10.1002/14651858.CD012563.pub2

299. Li X, Zhou M, Xia Q, Li J. Parecoxib sodium reduces the need for opioids after tonsillectomy in children: a double-blind placebo-controlled randomized clinical trial. Can J Anesth Can Anesth. 2016 Mar;63(3):268–74.

300. Bu X, Yang L, Zuo Y. Efficacy and safety of perioperative parecoxib for acute postoperative pain treatment in children: a meta-analysis. Front Med. 2015 Dec;9(4):496–507.

301. Yang W, Ming YC, Kau YC, Liao CC, Tsai SC, Wong KM, et al. A comparison of parecoxib and thoracic epidural analgesia for postoperative analgesia following Nuss procedure. J Pediatr Surg. 2015 Dec;50(12):2032–4.

302. Hullett B, Salman S, O'Halloran SJ, Peirce D, Davies K, Ilett KF. Development of a Population Pharmacokinetic Model for Parecoxib and Its Active Metabolite Valdecoxib after Parenteral Parecoxib Administration in Children. Anesthesiology. 2012 May 1;116(5):1124–33.

303. Tan L, Taylor E, Hannam JA, Salkeld L, Salman S, Anderson BJ. Pharmacokinetics and analgesic effectiveness of intravenous parecoxib for tonsillectomy ± adenoidectomy. Lerman J, editor. Pediatr Anesth. 2016 Dec;26(12):1126–35.

304. Armstrong P, Wilkinson P, McCorry NK. Use of parecoxib by continuous subcutaneous infusion for cancer pain in a hospice population. BMJ Support Palliat Care. 2018 Mar;8(1):25–9.

305. Thakerar A, Dines-Muntaner S, Trifunovich T, Alexander M, Fullerton S. Parecoxib as an adjunct therapy for the treatment of refractory non-surgical cancer pain. J Oncol Pharm Pract. 2020 Sep;26(6):1407–14.

306. Kenner DJ, Bhagat S, Fullerton SL. Daily Subcutaneous Parecoxib Injection for Cancer Pain: An Open Label Pilot Study. J Palliat Med. 2015 Apr;18(4):366–72.

307. Kellett E, Berman R, Morgan H, Collins J. Parecoxib for opioid-induced hyperalgesia. BMJ Support Palliat Care. 2021 Jun;11(2):126–7.

308. Jain P, Sharma S, Dua T, Barbui C, Das RR, Aneja S. Efficacy and safety of anti-epileptic drugs in patients with active convulsive seizures when no IV access is available: Systematic review and meta-analysis. Epilepsy Res. 2016 May;122:47–55.

309. Tulloch JK, Carr RR, Ensom MHH. A Systematic Review of the Pharmacokinetics of Antiepileptic Drugs in Neonates With Refractory Seizures. J Pediatr Pharmacol Ther. 2012 Aug 1;17(1):31–44.

310. Von Burg R, Stout T. Paraldehyde. J Appl Toxicol. 1991 Oct;11(5):379–81.

311. Jain P, Aneja S, Cunningham J, Arya R, Sharma S. Treatment of benzodiazepine-resistant status epilepticus: Systematic review and network meta-analyses. Seizure. 2022 Nov;102:74–82.

312. Hamilton Smith R, Eddleston M, Bateman DN. Toxicity of phosphate enemas-an updated review. Clin Toxicol. 2022 Jun 3;60(6):672–80.

313. NICE guidance. Constipation in Children and Young People: diagnosis and management. [Internet]. CG99 ed. https://www.nice.org.uk/guidance/cg99: NICE Clinical Guidance.; 2017. Available from: http://guidance.nice.org.uk/CG99

314. Landry BW, Fischer PR, Driscoll SW, Koch KM, Harbeck-Weber C, Mack KJ, et al. Managing Chronic Pain in Children and Adolescents: A Clinical Review. PM R. 2015/11/17 ed. 2015 Nov;7(11 Suppl):S295-315.

315. Pan Mersey Area Prescribing Committee. Pain in children: pharmacological management of chronic pain [Internet]. [cited 2023 May 29]. Available from: https://www.panmerseyapc.nhs.uk/media/2175/pain_children.pdf

316. Gale CK, Millichamp J. Generalised anxiety disorder in children and adolescents. BMJ Clin Evid. 2016 Jan 13;2016:1002.

317. Ke C, You X, Lin C, Chen J, Guo G, Wu W, et al. Development of Physiologically Based Pharmacokinetic Model for Pregabalin to Predict the Pharmacokinetics in Pediatric Patients with Renal Impairment and Adjust Dosage Regimens. J Pharm Sci. 2022 Feb;111(2):542–51.

318. Mann D, Antinew J, Knapp L, Almas M, Liu J, Scavone J, et al. Pregabalin adjunctive therapy for focal onset seizures in children 1 month to <4 years of age: A double-blind, placebo-controlled, video-electroencephalographic trial. Epilepsia. 2020 Apr;61(4):617–26.

319. Taghdiri MM, Bakhshandeh Bali MK, Karimzadeh P, Ashrafi MR, Tonekaboni SH, Ghofrani M. Comparative efficacy of zonisamide and pregabalin as an adjunctive therapy in children with refractory epilepsy. Iran J Child Neurol. 2015;9(1):49–55.

320. Kaul I, Amin A, Rosenberg M, Rosenberg L, Meyer WJ 3rd. Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: a retrospective chart review. Burns. 2017/08/22 ed. 2018 Mar;44(2):414–22.

321. Chan PLS, Marshall SF, McFadyen L, Liu J. Pregabalin Population Pharmacokinetic and Exposure-Response Analyses for Focal Onset Seizures in Children (4–16 years) and Adults, to Support Dose Recommendations in Children. Clin Pharmacol Ther. 2021 Jul;110(1):132–40.

322. Mann D, Liu J, Chew ML, Bockbrader H, Alvey CW, Zegarac E, et al. Safety, tolerability, and pharmacokinetics of pregabalin in children with refractory partial seizures: a phase 1, randomized controlled study. Epilepsia. 2014 Dec;55(12):1934–43.

323. Sato A, Saisho-Hattori T, Koizumi Y, Minegishi M, Iinuma K, Imaizumi M. Prophylaxis of Mucosal Toxicity by Oral Propantheline and Cryotherapy in Children with Malignancies Undergoing Myeloablative Chemo-Radiotherapy. Tohoku J Exp Med. 2006;210(4):315–20.

324. Christie DL, Ament M. Diagnosis and treatment of duodenal ulcer in infancy and childhood. Pediatr Ann. 1976 Nov;5(11):672–7.

325. Marshall S, Banting M. Propantheline for excess respiratory tract secretions in motor neuron disease. BMJ Support Palliat Care. 2023 Mar;13(1):63–4.

326. Ahmed T, Engelking C, Szalyga J, Helson L, Coombe N, Cook P, et al. Propantheline prevention of mucositis from etoposide. Bone Marrow Transplant. 1993 Aug;12(2):131–2.

327. Holmes DM, Montz FJ, Stanton SL. Oxybutinin versus propantheline in the management of detrusor instability. A patient-regulated variable dose trial. BJOG Int J Obstet Gynaecol. 1989 May;96(5):607–12.

328. Blaivas JG, Labib KB, Michalik SJ, Zayed AAH. Cystometric Response to Propantheline in Detrusor Hyperreflexia: Therapeutic Implications. J Urol. 1980 Aug;124(2):259–62.

329. Ekenved G, Magnusson A, Bodemar G, Walan A. Influence of Food on the Effect of Propantheline and L-hyoscyamine on Salivation. Scand J Gastroenterol. 1977 Dec;12(8):963–6.

330. Allahverdi B et al. Trial with prucalopride for colonic dysmotility in an Iranian child: A case presentation. Neurogastroenterol Motil. 2009;21(SUPPL. 1)(Conference abstract):77.

331. Carbone F, Van Den Houte K, Clevers E, Andrews CN, Papathanasopoulos A, Holvoet L, et al. Prucalopride in Gastroparesis: A Randomized Placebo-Controlled Crossover Study. Am J Gastroenterol. 2019 Aug;114(8):1265–74.

332. Coremans G, Kerstens R, De Pauw M, Stevens M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. Digestion. 2003;67(1–2):82–9.

333. Cuffari C, Spalding W, Achenbach H, Thakur M, Gabriel A. Design of a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of prucalopride in pediatric patients with functional constipation. Contemp Clin Trials Commun. 2023 Jun;33:101144.

334. Diederen K, Mugie SM, Benninga MA. Efficacy and safety of prucalopride in adults and children with chronic constipation. Expert Opin Pharmacother. 2015 Feb 11;16(3):407–16.

335. Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction-a double-blind, placebo-controlled, cross-over, multiple n = 1 study: Randomised clinical trial: prucalopride in chronic intestinal pseudo-obstruction. Aliment Pharmacol Ther. 2012 Jan;35(1):48–55.

336. Hirsch S, Nurko S, Mitchell P, Rosen R. Prucalopride for Treatment of Upper Gastrointestinal Symptoms in Children. Pediatr Drugs. 2022 Jan;24(1):73–81.

337. Jandee S, Wetwittayakhlang P, Boonsri P. Efficacy of prucalopride in critically ill patients with paralytic ileus: A pilot randomized double-blind placebo-controlled trial. J Gastroenterol Hepatol. 2021 Feb;36(2):362–6.

338. Krogh K, Jensen MB, Gandrup P, Laurberg S, Nilsson J, Kerstens R, et al. Efficacy and tolerability of prucalopride in patients with constipation due to spinal cord injury. Scand J Gastroenterol. 2002 Apr;37(4):431–6.

339. Motion J et al. Prucalopride for treatment refractory constipation in children: A single tertiary centre experience. J Pediatr Gastroenterol Nutr. 2022;74(2 Supplement 2)(Conference: 54th Annual Meeting of the European Society for Paediatric Gastroenterology Hepatology and Nutrition, ESPGHAN 2022. Copenhagen Denmark.):429–30.

340. Mutalib M, Kammermeier J, Vora R, Borrelli O. Prucalopride in intestinal pseudo obstruction, paediatric experience and systematic review. Acta Gastro Enterol Belg. 2021 Sep;84(3):429–34.

341. Piessevaux H, Corazziari E, Rey E, Simren M, Wiechowska-Kozlowska A, Kerstens R, et al. A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of long-term treatment with prucalopride. Neurogastroenterol Motil. 2015 Jun;27(6):805–15.

342. Redecillas S et al. Prucalopride in the treatment of paediatric chronic intestinal pseudo-obstruction Syndrome (CIPO). J Pediatr Gastroenterol Nutr. 2021;72(Suppl1)(Conference: 6th World Congress of Paediatric Gastroenterology, Hepatology and Nutrition. Vienna Austria.):507.

343. Santucci N et al. Effect of prucalopride in patients with functional constipation, gastroparesis, chronic nausea, chronic vomiting, and/or oesophageal dysmotility. J Pediatr Gastroenterol Nutr. 2021;73(Suppl1)(Conference: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting, NASPGHAN 2021. Virtual.):pp S447-S449.

344. Sloots CEJ, Rykx A, Cools M, Kerstens R, De Pauw M. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci. 2010 Oct;55(10):2912–21.

345. Vigone B, Caronni M, Severino A, Bellocchi C, Baldassarri AR, Fraquelli M, et al. Preliminary safety and efficacy profile of prucalopride in the treatment of systemic sclerosis (SSc)-related intestinal involvement: results from the open label cross-over PROGASS study. Arthritis Res Ther. 2017 Dec;19(1):145.

346. Yang T, Wang K, Cao Y, Wen J, Wei S, Li H, et al. Different doses of prucalopride in treating chronic idiopathic constipation: a meta-analysis and Bayesian analysis. BMJ Open. 2021 Feb;11(2):e039461.

347. Escobar-Serna DP et al. A case report of prucalopride treatment in pediatric gastroparesis: a novel therapy. Arch Argent Pediatr [Internet]. 2022 Apr 1 [cited 2023 Jun 18];120(2). Available from: https://www.sap.org.ar/docs/publicaciones/archivosarg/2022/v120n2a18e.pdf

348. Sridharan K, Sivaramakrishnan G. Drugs for Treating Opioid-Induced Constipation: A Mixed Treatment Comparison Network Meta-analysis of Randomized Controlled Clinical Trials. J Pain Symptom Manage. 2018 Feb;55(2):468-479.e1.

349. Nee J, Zakari M, Sugarman MA, Whelan J, Hirsch W, Sultan S, et al. Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2018 Oct;16(10):1569-1584.e2.

350. Siemens W, Gaertner J, Becker G. Advances in pharmacotherapy for opioid-induced constipation-a systematic review. Expert Opin Pharmacother. 2015 Mar;16(4):515–32.

351. Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2019 Nov;4(11):831–44.

352. Ginex P, Hanson B, LeFebvre K, Lin Y, Moriarty K, Maloney C, et al. Management of Opioid-Induced and Non–Opioid-Related Constipation in Patients With Cancer: Systematic Review and Meta-Analysis. Oncol Nurs Forum. 2020 Nov 1;47(6):E211–24.

353. Sadlonova M, Duque L, Smith D, Madva EN, Amonoo HL, Vogelsang J, et al. Pharmacologic treatment of delirium symptoms: A systematic review. Gen Hosp Psychiatry. 2022 Nov;79:60–75.

354. Campbell CT, Grey E, Munoz-Pareja J, Manasco KB. An Evaluation of Risperidone Dosing for Pediatric Delirium in Children Less Than or Equal to 2 Years of Age. Ann Pharmacother. 2019/11/28 ed. 2020 May;54(5):464–9.

355. Okamoto Y, Tsuneto S, Matsuda Y, Inoue T, Tanimukai H, Tazumi K, et al. A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients. J Pain Symptom Manage. 2007 Aug;34(2):217–22.

356. Grassi E, Latorraca S, Piacentini S, Marini P, Sorbi S. Risperidone in idiopathic and symptomatic dystonia: preliminary experience. Neurol Sci. 2000 Apr;21(2):121–3.

357. Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis. Pediatrics. 2016 Feb 1;137(Supplement_2):S124–35.

358. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Developmental, Psychosocial and Learning Problems Group, editor. Cochrane Database Syst Rev [Internet]. 2017 Aug 9 [cited 2023 May 29];2017(8). Available from: http://doi.wiley.com/10.1002/14651858.CD008559.pub3

359. Kenrick S (for Seeability). Treatment guidelines for symptom crises in Juvenile Battens Disease. 2011.

360. Bäckman ML, Berg LE, Aronen ET, Santavuori PR. New antidepressive and antipsychotic drugs in juvenile neuronal ceroid lipofuscinoses — a pilot study. Eur J Paediatr Neurol. 2001 Jan;5:163–6.

361. Capino AC, Thomas AN, Baylor S, Hughes KM, Miller JL, Johnson PN. Antipsychotic Use in the Prevention and Treatment of Intensive Care Unit Delirium in Pediatric Patients. J Pediatr Pharmacol Ther. 2020 Mar 1;25(2):81–95.

362. Liviskie C, McPherson C, Luecke C. Assessment and Management of Delirium in the Pediatric Intensive Care Unit: A Review. J Pediatr Intensive Care. 2023 Jun;12(02):094–105.

363. Khirani S, Dabaj I, Amaddeo A, Olmo Arroyo J, Ropers J, Tirolien S, et al. Effect of Salbutamol on Respiratory Muscle Strength in Spinal Muscular Atrophy. Pediatr Neurol. 2017 Aug;73:78-87 e1.

364. Frongia AL, Natera-de Benito D, Ortez C, Alarcón M, Borrás A, Medina J, et al. Salbutamol tolerability and efficacy in patients with spinal muscular atrophy type II. Neuromuscul Disord. 2019 Jul;29(7):517–24.

365. Hawley P, MacKenzie H, Gobbo M. PEG vs. sennosides for opioid-induced constipation in cancer care. Support Care Cancer. 2020 Apr;28(4):1775–82.

366. Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Cochrane Database Syst Rev. 2015;(5):CD003448.

367. McCullough RW. Practice insights on patient care-management overview for chemoradiation toxic mucositis-guidelines, guideline-supported therapies and high potency polymerized cross-linked sucralfate (ProThelial). J Oncol Pharm Pr. 2019 Mar;25(2):409–22.

368. Abtahi-Naeini B, Saffaei A, Sabzghabaee AM, Amiri R, Hosseini N, Niknami E, et al. Topical sucralfate for treatment of mucocutaneous conditions: A systematic review on clinical evidences. Dermatol Ther [Internet]. 2022 Apr [cited 2023 May 30];35(4). Available from: https://onlinelibrary.wiley.com/doi/10.1111/dth.15334

369. Kudaravalli P, John S. Sucralfate. [Internet]. 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551527/

370. Stevens B, Yamada J, Campbell-Yeo M, Gibbins S, Harrison D, Dionne K, et al. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. BMC Pediatr. 2018 Feb 23;18(1):85.

371. Li Q, Tan X, Li X, Tang W, Mei L, Cheng G, et al. Efficacy and safety of combined oral sucrose and nonnutritive sucking in pain management for infants: A systematic review and meta-analysis. Bhatt GC, editor. PLOS ONE. 2022 May 6;17(5):e0268033.

372. Vykol V, Wilson J, Goodwin J. Improving Consistency in the Use of Sucrose With Comfort Measures During Minor Painful Procedures. Adv Neonatal Care. 2023 Feb;23(1):10–6.

373. Sasidharan R, Gupta N, Yadav B, Chawla D, Singh K, Kumarendu Singh A. 25% Dextrose Versus 24% Sucrose for Heel Lancing in Preterm Infants: A Noninferiority RCT. Pediatrics. 2022 May 1;149(5):e2021054618.

374. Dickenson AH, Kress HG. Tapentadol: a new option for the treatment of cancer and noncancer pains. J Pain Res. 2019;12:1509–11.

375. Finkel JC, Goldberg J, Rosenburg R, Ariyawansa J, Sun T, Ochs-Ross R, et al. First evaluation of tapentadol oral solution for the treatment of moderate to severe acute pain in children aged 6 to <18. J Pain Res. 2019;12:1925–36.

376. Freo U, Romualdi P, Kress HG. Tapentadol for neuropathic pain: a review of clinical studies. J Pain Res. 2019;12:1537–51.

377. Kress HG, Coluzzi F. Tapentadol in the management of cancer pain: current evidence and future perspectives. J Pain Res. 2019;12:1553–60.

378. Muse D, Tarau E, Lefeber C, Sohns M, Brett M, Goldberg J, et al. Pharmacokinetics, safety, and efficacy of tapentadol oral solution for treating moderate to severe pain in pediatric patients. J Pain Res. 2019;12:1777–90.

379. Wiffen PJ, Derry S, Naessens K, Bell RF. Oral tapentadol for cancer pain. Cochrane Database Syst Rev. 2015 Sep 25;(9):CD011460.

380. Farrer E, Dickman A. New analgesics in cancer pain. Curr Opin Support Palliat Care. 2022 Jun;16(2):60–4.

381. Freynhagen R, Elling C, Radic T, Sohns M, Liedgens H, James D, et al. Safety of tapentadol compared with other opioids in chronic pain treatment: network meta-analysis of randomized controlled and withdrawal trials. Curr Med Res Opin. 2021 Jan 2;37(1):89–100.

382. Dai AI, Aksoy SN, Demiryurek AT. Comparison of Efficacy and Side Effects of Oral Baclofen Versus Tizanidine Therapy with Adjuvant Botulinum Toxin Type A in Children With Cerebral Palsy and Spastic Equinus Foot Deformity. J Child Neurol. 2016 Feb;31(2):184–9.

383. Henney HR 3rd, Chez M. Pediatric safety of tizanidine: clinical adverse event database and retrospective chart assessment. Paediatr Drugs. 2009;11(6):397–406.

384. Palazon Garcia R, Benavente Valdepenas A, Arroyo Riano O. [Protocol for tizanidine use in infantile cerebral palsy]. Pediatr Barc. 2008 May;68(5):511–5.

385. Spiller HA, Bosse GM, Adamson LA. Retrospective review of Tizanidine (Zanaflex) overdose. J Toxicol Clin Toxicol. 2004;42(5):593–6.

386. Kluger M, Penrose S, Bjorksten AR, Chalkiadis G. Accuracy of dispersing tramadol capsules for oral administration in young children. Anaesth Intensive Care. 2016 Nov;44(6):742–4.

387. Rodieux F, Vutskits L, Posfay-Barbe KM, Habre W, Piguet V, Desmeules JA, et al. When the Safe Alternative Is Not That Safe: Tramadol Prescribing in Children. Front Pharmacol. 2018/03/21 ed. 2018;9:148.

388. Li S, Xiong H, Jia Y, Li Z, Chen Y, Zhong L, et al. Oxycodone vs. tramadol in postoperative parent-controlled intravenous analgesia in children: a prospective, randomized, double-blinded, multiple-center clinical trial. BMC Anesthesiol. 2023 May 3;23(1):152.

389. Yoo O, Tang EKY, Salman S, Nguyen MN, Sommerfield D, Sommerfield A, et al. A randomised controlled trial of a novel tramadol chewable tablet: pharmacokinetics and tolerability in children. Anaesthesia. 2022 Apr;77(4):438–48.

390. Yaffe Ornstein M, Stocki D, Levin D, Dvir R, Manisterski M, Berger-Achituv S, et al. Tramadol Treatment for Chemotherapy-induced Mucositis Pain in Children. J Pediatr Hematol Oncol. 2022 Mar;44(2):e487–92.

391. Wang L, Guo Y, Tian J. The comparison of ketamine with tramadol for postoperative pain relief on children following adenotonsillectomy or tonsillectomy: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2021 Apr 9;100(14):e22541.

392. Fortenberry M, Crowder J, So TY. The Use of Codeine and Tramadol in the Pediatric Population—What is the Verdict Now? J Pediatr Health Care. 2019 Jan;33(1):117–23.

393. Calligaris L, Marzuillo P, Barbi E. Re: Tramadol can selectively manage moderate pain in children following European advice limiting codeine use. Acta Paediatr. 2014 Nov;103(11):e466.

394. Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ. Tranexamic acid for patients with nasal haemorrhage (epistaxis). Cochrane ENT Group, editor. Cochrane Database Syst Rev [Internet]. 2018 Dec 31 [cited 2023 May 30];2018(12). Available from: http://doi.wiley.com/10.1002/14651858.CD004328.pub3

395. Saini AG, Hassan I, Sharma K, Muralidharan J, Dhawan S, Saini L, et al. Status Dystonicus in Children: A Cross-Sectional Study and Review of Literature. J Child Neurol. 2022 May;37(6):441–50.

396. Treillet E, Laurent S, Hadjiat Y. Practical management of opioid rotation and equianalgesia. J Pain Res. 2018 Oct;Volume 11:2587–601.

397. De Iaco F, Mannaioni G, Serra S, Finco G, Sartori S, Gandolfo E, et al. Equianalgesia, opioid switch and opioid association in different clinical settings: a narrative review. Eur Rev Med Pharmacol Sci. 2022 Mar;26(6):2000–17.

398. Shrestha S, Khatiwada AP, Sapkota B, Sapkota S, Poudel P, Kc B, et al. What is "Opioid Stewardship"? An Overview of Current Definitions and Proposal for a Universally Acceptable Definition. J Pain Res. 2023 Feb;Volume 16:383–94.

399. Hardy JR, Bundock D, Cross J, Gibbons K, Pinkerton R, Kindl K, et al. Prevalence of QTc Prolongation in Patients With Advanced Cancer Receiving Palliative Care-A Cause for Concern? J Pain Symptom Manage. 2020 Apr;59(4):856–63.

400. Walker G, Wilcock A, Carey AM, Manderson C, Weller R, Crosby V. Prolongation of the QT interval in palliative care patients. J Pain Symptom Manage. 2003 Sep;26(3):855–9.

401. Toth C. Substitution of Gabapentin Therapy with Pregabalin Therapy in Neuropathic Pain due to Peripheral Neuropathy. Pain Med. 2010 Mar;11(3):456–65.

402. Bockbrader HN, Budhwani MN, Wesche DL. Gabapentin to Pregabalin Therapy Transition: A Pharmacokinetic Simulation. Am J Ther. 2013 Jan;20(1):32–6.

403. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain. 2020 May;14(2):104–14.

404. Irwin MN, Quirk K, Banner A, Hosseini K, Smith MA. Strategies for Rotation between Gabapentinoids in the Inpatient Setting. J Pain Palliat Care Pharmacother. 2021 Jan 2;35(1):13–22.

405. Ifuku M, Iseki M, Hidaka I, Morita Y, Komatus S, Inada E. Replacement of Gabapentin with Pregabalin in Postherpetic Neuralgia Therapy. Pain Med. 2011 Jul;12(7):1112–6.

406. NHS Scotland. Neuropathic pain [Internet]. Scottish Palliative Care Guidelines. 2022 [cited 2023 Jul 9]. Available from: https://www.palliativecareguidelines.scot.nhs.uk/guidelines/pain/neuropathic-pain.aspx

407. Montero-Padilla S, Velaga S, Morales JO. Buccal Dosage Forms: General Considerations for Pediatric Patients. AAPS PharmSciTech. 2017 Feb;18(2):273–82.

408. Lam JKW, Xu Y, Worsley A, Wong ICK. Oral transmucosal drug delivery for pediatric use. Adv Drug Deliv Rev. 2014 Jun;73:50–62.

409. Goyal AK, Singh R, Chauhan G, Rath G. Non-invasive systemic drug delivery through mucosal routes. Artif Cells Nanomedicine Biotechnol. 2018 Nov 5;46(sup2):539–51.

410. UK Medicines Information pharmacists. How should medicines be dosed in children who are obese? [Internet]. UK Specialist Pharmacy Service. 2021 [cited 2023 Aug 11]. Available from: https://www.sps.nhs.uk/articles/how-should-medicines-be-dosed-in-children-who-are-obese/

The Association for Paediatric Palliative Medicine Formulary

6th edition 2024

The definitive guide to prescribing in paediatric palliative medicine

The APPM Formulary brings together all available paediatric palliative care prescribing information in a single volume, utilising up to date research evidence and consensus expert opinion.

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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.