Mild Opiate Analgesia: Safe Use, Contraindications and Recommended Alternatives
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A Clinical Guideline recommended

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1.1	March 2016	Addition of disclaimer on footer on front page	Codeine Working Group on behalf of the DTMM Committee
2	April 2018	Document reviewed and no changes made at this time.	Codeine Working Group on behalf of the DTMM Committee
2.1	April 2021	Three month extension given.	Codeine Working Group on behalf of the DTMM Committee
2.2	October 2021	Extension pending review.	Codeine Working Group on behalf of the DTMM Committee
2.3	January 2022	Further extension pending review.	Codeine Working Group on behalf of the DTMM Committee
3	October 2022	Title amended to reflect content more appropriately, updated to paediatric doses.	Codeine Working Group on behalf of the DTMM Committee

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1. Objective

To provide clinical guidance to all prescribers to ensure safe and appropriate use of Mild Opiate Analgesia.

The guidelines set out specific recommendations for 3 groups:

1. Any patient who is or may be a codeine "ultra-rapid" metaboliser, and who is consequently at risk of opiate toxicity.
2. Children and adolescents.
3. Women in late pregnancy, or who are breastfeeding.

2. Rationale

In June 2013, the MHRA placed restrictions on the use of codeine following several codeine-related deaths in breast-fed infants, children and teenagers. The restrictions principally apply to children and young adults (<19y), breast-feeding women, and any patient who is a codeine "Ultra-rapid Metaboliser".

Codeine is a widely used opioid analgesic and is sometimes given post-operatively for pain relief in children. Codeine has a very low affinity for opioid receptors and is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6).

Genetic differences in the expression of the CYP2D6 enzyme results in differences in the extent to which codeine is metabolised. Patients deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not obtain adequate analgesic pain relief. Conversely, patients who metabolise codeine very rapidly (ultra-rapid metabolisers) are at increased risk of developing adverse effects of opioid toxicity, even at low doses.

Dihydrocodeine is similar to codeine in both its structure and analgesic effect. Although it is primarily metabolised to dihydromorphine and nordihydrocodeine, it is unclear whether the parent drug, metabolites or a combination of both results in its analgesic activity. **This makes dihydrocodeine safer in patients who are ultrarapid metabolisers of codeine and more effective in those who are poor metabolizers of codeine.**

There is significant ethnic variation in the prevalence of rapid and slow metabolisers (see Table 1).

Table 1: Incidence of Ultra-rapid Metabolisers for different ethnic Groups.

Population	Incidence of Ultra-rapid Metabolisers	Notes
African (especially Ethiopians)	29.0%	Codeine and Dihydrocodeine CONTRAINDICATED
African American	3.4-8.9%	Use with caution
Asian	1.2-2.0%	Note there is a high incidence of *slow* metabolisers in patients of Far Eastern origin – codeine more likely to be ineffective.
Caucasian	3.6-6.5%	Codeine may be used in patients not falling into one

Greek	6.0%	of the “at-risk” groups. Note that the incidence of ultra-rapid metabolisers is higher in patients of Southern European origin.
Hungarian	1.9%	
Northern European	1.0-2.0%	

3. Ultra-Rapid Metabolisers (any age)

3.1 Guidance

Patients with a Previous Adverse Reaction to codeine or dihydrocodeine

- For patients with a previous adverse reaction to codeine or dihydrocodeine, DO NOT USE codeine or dihydrocodeine. Note that codeine- and dihydrocodeine-containing analgesics are available in "over the counter" combination preparations.

Patients likely to be 'Ultra-rapid' metabolisers

- Patients of Black African or Ethiopian ethnicity have a very high incidence of ultra-rapid metabolisers. Codeine or dihydrocodeine should not be used in these patients and only with caution in those of African-American origin or southern European origin, (see Table 1).

Note: Codeine is commonly ineffective in patients of Far Eastern ethnicity and alternative analgesia is recommended (see table 1).

3.2 Alternatives to Codeine in Adults (19 years or over)

- Where possible, optimise simple analgesia (e.g. Paracetamol, ibuprofen). If appropriate consider regular, rather than "as required" administration. Note that in some patients, NSAIDs are inadvisable.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the patient's distress.
- Intravenous and rectal paracetamol are options, where the oral route is not available and the patient has IV access. Note that the total dose of paracetamol given by all routes should not exceed the maximum permitted dose in a 24 hour period.
- Where simple analgesia and other measures are not adequate, it is appropriate to use opiates for breakthrough pain. Consider whether oral analgesia will be sufficient and timely. If so, oral morphine is the opiate of choice.

For patients with uncontrolled *moderate* pain, despite oral analgesia, or where this has been ineffective, parenteral (IM or IV) morphine is recommended.

Guidance on equivalent doses of alternative opiates may be found here: Opiate Conversion Card *(also on the Pain Management Service Web page*)

- Where morphine is contraindicated or ineffective, contact the Pain Team for advice.

4. Children and Adolescents

Additional guidance on management of pain in children and adolescents may be found in the following guidelines:

Pain in Neonates, Infants, Children and Adolescents

Patient Controlled Analgesia (PC) or Nurse Controlled Analgesia (NCA) in Children

Children receiving Epidural Analgesia

4.1 Guidance

4.1.1 Children under 12 years of age

- Codeine **must not be** used in children under 12 years of age.

4.1.2 Children and Adolescents 12-18 years

Indication

- Codeine should only be used in to relieve acute, moderate pain, and only if it cannot be relieved by use of simple analgesics such as paracetamol or ibuprofen.

Contraindications

- Children with a previous adverse reaction to codeine, or from a high-risk ethnic group.
- Codeine is contraindicated in all patients who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea.
- Codeine is not recommended for use in children and adolescents 12–18 years, in children at significant risk of respiratory compromise. Consider risks on a case-by-case basis.
    - Children at risk of respiratory compromise may include those with morbid obesity, neuromuscular disorders such as Duchenne Muscular Dystrophy, children on long-term oxygen therapy, those with severe respiratory infections, etc. Note that this list is not exhaustive. The risk of opiate toxicity may be increased in these settings.

Frequency, dose and duration

- The maximum daily dose should not exceed 240 mg. This may be taken in divided doses, up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period.
- Duration of treatment should be limited to 3 days and if not effective medical review is required.

Information for Patients and Parents/Caregivers

- The *Codeine Phosphate for Pain Information Sheet*, http://www.medicinesforchildren.org.uk/search-for-a-leaflet/codeine-phosphate-for-pain/, should be given to parents and caregivers. It gives guidance on how to recognise the signs of opiate toxicity.
- Symptoms of opiate toxicity include:
    - Reduced levels of consciousness
    - Excessive somnolence
    - Respiratory depression
    - ‘Pin-point’ pupils
    - lack of appetite
    - nausea and vomiting
- Codeine MUST be stopped if any symptoms of toxicity occur, and medical attention must be sought immediately.

4.2 Alternatives to Codeine in Children and Adolescents (<19 years)

Alternatives for Hospital Use

- Where possible, optimise simple analgesia (e.g. paracetamol, ibuprofen). If appropriate consider regular, rather than "as required" administration. Note that in some patients, NSAIDs such as ibuprofen are inadvisable. Note this is relatively rare in children.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the patient's distress.
- Intravenous or rectal paracetamol are appropriate options, where simple oral analgesia is not effective, or the oral route is not available and the patient has IV access. Note that the total dose of paracetamol given by all routes should not exceed the maximum permitted dose in a 24 hour period.
- Where simple analgesia and other measures are not adequate, it is appropriate to use opiates for breakthrough pain. Consider whether oral analgesia will be sufficient and timely. If so, oral morphine is the opiate of choice. (See Trust Guideline, October 2020, "Management of pain in Neonates, children and adolescents" JCG0014, Trust Docs ID 8799.)
- For patients with uncontrolled *moderate* pain, despite oral analgesia, or where this has been ineffective, parenteral (IM or IV) morphine is recommended (see suggested doses below). Consider involving the pain team.
- For patients with *severe* pain IV morphine or intranasal Diamorphine (for patients lacking IV access) is suitable (typically in the emergency situation).

JCG0014, Trust Docs ID 8799 – suggested oral morphine dose

Oral Analgesic	Age	Dose	Maximum	Frequency
Morphine sulphate (Oramorph)	6 months – 1 year	100 - 200 micrograms/kg	200 micrograms/kg	4 hourly / as required
	> 1year	100 – 400 micrograms/kg	400 micrograms/kg	

JCG0014, Trust Docs ID 8799 – suggested IV/IM dose morphine, intranasal diamorphine

Analgesics	Route	Dose	Frequency
Morphine sulphate	IV loading dose IV or SC infusion	50 – 100 micrograms/kg loading 10 – 20 micrograms/kg/hour* (*higher doses, to max of 40	Titrated to response over at least 5 minutes.

		micrograms/kg/hr may be used in patients who are ventilated)	Can repeat IV dose after 10 minutes
Diamorphine Child > 10 kg	Intranasal	100 micrograms/kg	Usually one dose *See protocol appendix*

Alternatives for TTO/home use

- Patients should be advised to avoid codeine/dihydrocodeine-containing medication.
- Where possible, optimise simple analgesia (e.g. paracetamol, ibuprofen). If appropriate consider regular, rather than "as required" administration.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the patient's distress.
- For patients who are intolerant of oral paracetamol (e.g. vomiting or refusal in young children) rectal administration may be appropriate. Note that the total dose of paracetamol given by all routes should not exceed the maximum permitted dose in a 24 hour period.
- Where necessary, oral morphine can be supplied as a TTO. The number of doses or duration of therapy must be stated. Note that the addictive potential of oral morphine solution (10mg/5mL) is minimal.

4.3 Guidance on Oral Morphine Solution TTOs for Children (<18 years)

Aim

- To facilitate the effective and safe prescription of TTO Morphine Sulphate 10mg/5mL post-operatively.

Indications

- For the management of moderate post-operative pain at home in children who may previously have received codeine.

Contraindication

- TTO oral morphine solution should not be prescribed to patients at risk of respiratory depression or increased sensitivity to opiates e.g.: patients with a history of obstructive sleep apnoea, patients with airway abnormalities, patients with a reduced respiratory reserve and infants or children under 10kg.

Prescription

- TTO oral morphine solution should be prescribed in a reduced dose compared with in-hospital use, because of the lack of immediate monitoring, oxygen and availability of immediate life support, in the event of respiratory depression.
- Prescribe "as required", not as a regular prescription. A suitable dose for use at home is 100-150 microgram /kg. e.g. for a 20kg child, the dose would usually be 2 to 3 mg.
- In certain circumstances, a higher dose, 200 microgram/kg, (max 10mg) may be prescribed.

- The dose should be rounded to the nearest whole number in milligrams to make administration easier for parents and reduce the risk of error.
- e.g. for a 24kg child, prescribe 3mg rather than 2.4mg or 3.6mg.
- Specify Oral Morphine Solution, 10mg/5mL.
- The dose should be reduced in children with a high BMI to a dose appropriate to their age.
- The maximum frequency of administration is 6 hourly.
- The total volume dispensed will not usually exceed 20mL. However in older children this may be increased to 40mL. Where the patient's consultant believes longer treatment is required, (for example after major orthopaedic procedures such as femoral osteotomy) up to 2 weeks' supply may be given.
- Clear verbal and written instructions should be given to parents, outlining the dose in millilitres (mL), the minimum interval of 6 hours between doses, that it should only be used on an as required basis to relieve pain that is not controlled with paracetamol and/or ibuprofen, the symptoms/signs of overdose, instructions in the event of suspect overdose, disposal instructions and contact numbers.

5. Late Pregnancy and Breastfeeding

Further guidance on management of pain in labour may be found in the following patient information leaflet/guidelines:

Pain Relief In Labour (M49 (v2))

Labour Intrapartum Analgesia with IV PCA Using Remifentanil (CA2062 V3)

Epidural Analgesia in Labour (CA4054 v2)

Inadequate treatment of postnatal pain has serious implications and regular postnatal analgesia is therefore important. Inadequately controlled pain can mean women are less mobile, which increases their risk of venous thromboembolism, they are also more prone to shallow breathing, which puts them at risk of developing pneumonia. It may also impact negatively on the woman's ability to breastfeed or care for her new infant and may contribute to depression or mental exhaustion.

5.1 Guidance

- Codeine should be avoided, if at all possible, in late pregnancy, labour and in breastfeeding mothers because it can pass to the baby through the placenta or breast milk and potentially cause harm.
- If paracetamol and NSAIDs (if able to give) do not provide sufficient pain relief after caesarean birth, consider adding dihydrocodeine to paracetamol (and NSAID if able to take), or changing to co-dydramol (combination preparation of paracetamol and dihydrocodeine) as an alternative to paracetamol.
- Advice from UK Medicines Information (UKMi) is that dihydrocodeine, in the breastfeeding mother should be at the lowest effective dose for the shortest duration.

- Regular use of any opioid beyond 3 days should be under close medical supervision.
- All breastfeeding mothers, regardless of ethnicity, should be informed of the potential problems and advised to stop breastfeeding if symptoms develop and seek medical advice.
- All breastfed infants should be monitored for opioid adverse effects regardless of the maternal dose. If significant opioid adverse effects develop in the mother, this could suggest the possibility that she is an ultra-rapid metaboliser and that the risk of adverse effects in the infant may be increased.
- Women with a previous adverse reaction to codeine, or from a high-risk ethnic group should not receive codeine or dihydrocodeine.

5.2 Alternatives to codeine in late pregnancy & breastfeeding

5.2.1 Analgesic Choices

- Analgesic choices should ideally be discussed and documented with the woman in advance of labour, delivery and breastfeeding.
- Drug pharmacokinetics in the newborn infant differs from adults. Opiate analgesia administered within 48 hours of delivery has the potential to harm the infant. Similarly opiates administered to breast-feeding mothers may have harmful or fatal consequences for the infant.

5.2.2 Analgesia in Labour

Note that Codeine is *not suitable for use as analgesia in labour*. Consult appropriate obstetric guidelines for analgesia in labour: Pain Relief in Labour (M49 (v2))

5.2.3 Alternatives to Codeine in Late Pregnancy where Delivery is Anticipated Within 48 hours (for women who are not in Labour)

- Where analgesia is required, if possible use paracetamol. If appropriate consider regular, rather than "as required" administration.
- Note that non-steroidal anti-inflammatory drugs, such as ibuprofen are not recommended in the third trimester of pregnancy.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the woman's distress.

5.2.4 Where Opiates are required

- If use of codeine is thought necessary in late pregnancy, the period of exposure should be as brief as possible.
- Where parenteral opiates are required for a pregnant woman not in labour, the preferred agent is morphine. Morphine is preferred to pethidine.
- Morphine and pethidine cross the placenta, and their effects on the foetus are dependent on dose and timing of administration.
- Infants born to mothers who have received opiates in labour or within 48 hours of birth have been shown to be sleepier, less attentive, and less able to establish breast feeding. Mothers intending to breastfeed will require additional support to facilitate successful feeding (see Management of Healthy Babies over 37 weeks gestation who are Reluctant to Feed (MID35v2).

5.2.5 Alternatives to Codeine for Use in Breast-feeding Mothers

- Breastfeeding provides optimal nutrition for the infant and has health benefits for both mother and child. Nursing mothers should be advised to avoid codeine.
- Where possible, optimise simple analgesia (e.g. paracetamol, ibuprofen). If appropriate consider regular, rather than "as required" administration.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the patient's distress.

5.2.6 Where Opiates are required

- Where simple analgesia and other measures are not adequate, it is appropriate to use opiates for breakthrough pain. Consider whether oral analgesia will be sufficient and timely. If so, oral morphine is the opiate of choice.
- For inpatients with uncontrolled moderate pain, despite oral analgesia, or where this has been ineffective, parenteral (IM or IV) morphine is recommended. The obstetric anaesthetist will advise on management where oral morphine has proved insufficient.

5.2.7 TTO/home use

- The majority of women requiring analgesia on discharge should receive paracetamol and ibuprofen (unless there are contraindications to NSAIDs). If additional analgesia is required, for example, if a woman is discharged 1–2 days post lower segment caesarean section as part of an enhanced recovery programme and is still requiring oral morphine solution in hospital or cannot take NSAIDs, she should be discharged with a limited supply of dihydrocodeine to take as required (maximum of 30mg four times per day, 14 x 30mg tablets). Oramorph may be considered if a woman is known to be intolerant to dihydrocodeine.

6. Compliance Monitoring

Compliance to the guideline will be monitored through medication incident reports.

Incidents involving codeine will be reported to the DTMM Committee, with appropriate actions being determined, depending on the nature of the incident. If appropriate, the incident will be additionally reported to the Clinical Safety Executive Sub-Board.

7. Summary of development and consultation process

Guideline on Safe Use of Codeine Analgesia was developed by the Codeine Working Group on behalf of the DTMM Committee.

Membership of Codeine Working Group

Name	Role
Dr Ajay Arora	Consultant Paediatric Anaesthetist
Alice Cook	Registered Nurse (Child)
Dr Jeremy Corfe	Consultant Obstetric Anaesthetist
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Mrs Debbie Upton	Paediatric Practice Development Nurse
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Dr Kathy Wilkinson	Consultant Paediatric Anaesthetist
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The guideline was developed by the Codeine Working Group and circulated to the DTMM Committee, Paediatric Pain Group, anaesthetic, obstetric and orthopaedic departments and Jenny Lind Children's Hospital Governance Committee, with comments being incorporated into the final draft.

During review in 2018 the guideline was circulated for comment to members of the original Working Group and also to Dr Jasmine Kaur (Consultant Anaesthetist and paediatric acute pain lead) and Mrs Rebecca Turner (Practice Development Nurse, Paediatrics).

During review in 2021/2 the guideline was circulated for comment to members of the original Working Group and also to Dr Jasmine Kaur (Consultant Anaesthetist and paediatric acute pain lead), Miss Nicola Rudge (Chief Pharmacist), and Dr Aravind Shastri (Service Director, Paediatrics).

8. Distribution List/ Dissemination Method

Published on Trust Intranet with links from appropriate departmental guideline pages.

9. References

1. MHRA Guidance: Drug Safety Update; 6(12), July 2013: A1.

2. European Medicines Agency Pharmacovigilance Risk Assessment Committee; PRAC recommends restricting the use of codeine when used for pain relief in children, EMA/350259/2013.

3. Whittaker MR. Opioid Use and the Risk of Respiratory Depression and Death in the Pediatric Population. J Pediatr Pharmacol Ther. 2013 Oct;18(4):269-276. Review.

4. Royal College of Anaesthetists, Association of Paediatric Anaesthetists of Great Britain and Ireland and the Joint Medicines Committee of the Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group. Guidance for the use of codeine in children. November 2013 https://www.apagbi.org.uk/sites/default/files/paragraphs/files/Codeine_Nov2013.pdf

5. Bisson DL, Newell SD, Laxton C, on behalf of the Royal College of Obstetricians and Gynaecologists. Antenatal and Postnatal Analgesia. Scientific Impact Paper No. 59. BJOG 2019;126:e115–24.

6. Wojciech Leppert & Jarosław Woroń (2016) Dihydrocodeine: safety concerns, Expert Review of Clinical Pharmacology, 9:1, 9-12, DOI: 10.1586/17512433.2016.1092871.

7. Caesarean birth, NICE guideline NG192 Published 31 March 2021

10. Equality Impact Assessment

This guideline has been screened to determine equality relevance for the following equality groups: race, gender, age sexual orientation and religious groups. This guideline is considered to have no equality relevance.