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

For Use in:	Norfolk and Norwich University Hospitals NHS Foundation Trust
By:	The Drugs, Therapeutics and Medicines Management (DTMM) Committee
For:	All Prescribers
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If Yes - does the strategy/policy deviate from the recommendations of NICE? **If so why?**	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

Objective

To provide clinical guidance to all prescribers to ensure safe and appropriate use of codeine for 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.

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 indicated for persistent pain of moderate intensity. It is converted to morphine by the hepatic enzyme CYP2D6. Metabolism of codeine is highly variable between individuals. Some patients have ultra-rapid metabolism of codeine with the potential for opiate toxicity. Furthermore, a significant proportion of patients ("slow metabolisers") do not achieve effective analgesia with 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 of the “at-risk” groups. Note that the incidence of ultra-rapid metabolisers is higher in patients of Southern European origin.
Greek	6.0%	
Hungarian	1.9%	
Northern European	1.0-2.0%	

1.0 Ultra-Rapid Metabolisers (any age)

1.1 Guidance

Patients with a Previous Adverse Reaction to Codeine

- 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 "over the counter".

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).

- Codeine is commonly ineffective in patients of Far Eastern ethnicity and alternative analgesia is recommended

1.2 Alternatives to Codeine in Adults (19years 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 Paracetamol is an appropriate option, 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.

  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.

2. 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

2.1 Guidance

Children under 12 years of age

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

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*, provided by pharmacy, 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

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

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.
- Consider other specific symptomatic treatment (e.g. positioning, anti-emetics), to alleviate factors contributing to the patient's distress.
- Intravenous paracetamol is an appropriate option, 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.
- For patients with uncontrolled *moderate* pain, despite oral analgesia, or where this has been ineffective, parenteral (IM or IV) morphine is recommended. 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).

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.

2.3 Guidance on Oral Morphine Solution TTOs for Children (<18y)

Aim

- To facilitate the effective and safe prescription of TTO Oramorph 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 eg: 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 supplied.
- 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. In addition, pharmacy will provide a patient information sheet: [link to NNUH PIL be inserted].

3. 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)

3.1 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.
- Women with a previous adverse reaction to codeine, or from a high risk ethnic group should not receive codeine or dihydrocodeine.

3.2. Alternatives to Codeine

3.2.1 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.

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))

3.2.2 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 pregnancy.
- Consider other specific symptomatic treatment (eg positioning, anti-emetics), to alleviate factors contributing to the woman's distress.

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).

3.2.3 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 or dihydrocodeine-containing medication (including over-the-counter 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.

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.

Opiates for TTO/home use

- For outpatients with uncontrolled *moderate* pain, despite optimising oral analgesia, or where this has been ineffective, oral morphine solution is recommended. Where these measures do not prove sufficient, specialist advice should be sought.

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.

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
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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).

Distribution list / dissemination method

Codeine Analgesia: Safe Use, Contraindications and Recommended Alternatives
Published on Trust Intranet with links from appropriate departmental guideline pages.

References

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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

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.