British Association of Perinatal Medicine

Management of Neonatal Pain

A DRAFT Framework for Practice

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Executive Summary

Neonates even at the lowest limit of viability, have profound acute reactions to noxious stimuli. It is not possible to eliminate painful procedures in hospital and it may not be possible to relieve all the pain that a neonate undergoes, but given the cumulative evidence surrounding the burden of pain in neonates *(Carbajal 2008)*, and growing concerns regarding potential long-term neurodevelopmental effects of pain in early life (Valeri 2015), appropriate and effective management of pain must be integrated into neonatal care.

Summary

Families expect health care professionals to recognise, measure, prevent and treat pain in neonates, and health care professionals have a duty of care in this respect, especially in view of the adverse long-term effects of early pain exposure.

1. An evidence-based guideline for managing pain should be adopted by all neonatal units.
2. Parents and carers should be actively involved in planning of procedures and providing non-pharmacological pain management.
3. Exposure to noxious stimuli should be minimised.
4. Objective and validated pain tools/scale should be used to measure pain caused by procedures and to guide treatment of ongoing pain.
5. Health care professionals should be trained to measure and treat pain, and to include parents in pain management.
6. A multimodal tiered approach should be used to measure and treat neonatal pain.
7. Pre-emptive use of appropriate combinations of non-pharmacological approaches and analgesic medications should be used to treat acute episodic pain.
8. Non-pharmacological support for babies should be provided by parents, or by health care professionals when parents cannot be present.
9. Pharmacological treatment should be used judiciously and in conjunction with non-pharmacological techniques.
10. Routine use of opioid infusions as analgosedative in mechanically ventilated neonates particularly if extremely preterm is discouraged.
11. Where necessary, intermittent boluses of opioids titrated to the degree of pain is favoured compared to continuous opioid infusion.
12. Management of prolonged pain is challenging, and a combination of non-pharmacological and pharmacological approaches is recommended, with parents playing a key role.
13. Continuous infusion of Benzodiazepines are contra-indicated for use in preterm babies.
14. Awareness of measures to avoid or delay opioid tolerance should be embedded in practice.
15. Further research is needed into measuring pain and optimising treatments.

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Aims

Families expect health care professionals to recognise, measure, prevent and treat pain in neonates, and health care professionals have a duty of care in this respect, especially in view of the adverse long-term effects of early pain exposure. Therefore, each neonatal service must establish guidelines and protocols to measure and treat pain, which include the use of non-pharmacological and pharmacological analgesic therapy.

This framework is intended as best practice guidance for all health care professionals working in neonatal services to help inform the development of local guidelines to support the management of neonatal pain.

Purpose and target audience

Health care professionals who care for term and pre-term neonates in the neonatal unit or in an outreach setting.

Scope

The scope and content of this document were determined by members of the working group. Development of this framework was consensus based, when there was a lack of available robust evidence. Relevant literature and existing national policies and guidelines were considered on key topics, and where evidence was available it has been used to support the recommendations in this framework. The group met by video conference to respond to points raised during consultation as well as conducting meetings with members of various professional groups prior to producing this framework. The framework does not cover analgesic use during endotracheal intubation (covered in BAPM Neonatal Airway Safety Standard), operative procedures and redirection of care.

Language

The British Association of Perinatal Medicine is committed to continuously fostering a diverse environment. We acknowledge the effect language can have on individuals and populations. This guidance makes recommendations for women and people who are pregnant and breast feeding. For simplicity of language, the guideline uses the terms women and mothers throughout but this should also be taken to include people who do not identify as women but who are pregnant, labour and in the postnatal period. The term breastfeeding is also used but should be taken to include those who term this method of feeding as chest or body feeding. When discussing with a person who does not identify as woman, please ask them their preferred pronouns and terminology. We also acknowledge that we may not get the language right every time, and welcome feedback on our work.

Introduction

Pain is defined as an "unpleasant sensory or emotional experience associated with actual or potential tissue damage or perceived in terms of such damage" (Raja 2020, IASP).

Neonates experience varying degrees of pain, discomfort or stress, resulting from invasive procedures that occur during routine care and from pathological conditions. They can be exposed to multiple painful procedures daily (Cruz 2016). This exposure to repeated pain in early life can contribute to prolonged pain (Van Ganzewinkel 2014), short-term physiological instability and can cause primary hyperalgesia, peripheral hypersensitivity, lowered pain thresholds and hypersensitivity to pain (Slater 2012, Walker 2014, Valerie 2015).

The paradigm of brain injury in the preterm neonates is shifting from a 'one-hit brain injury' to overall alteration in trajectory of brain maturation which occurs with 'everyday' clinical exposures (Back 2014). Pain is part of 'everyday' clinical exposure and an important modifiable adverse factor in the NICU (Ranger 2013, Chau 2019, Vinall 2014). It has long-term neurodevelopmental consequences (Boggini 2021, Williams and Lascelles 2020, Cong 2017) such as reduced growth, altered structural and functional brain development (Doesburg 2013), and effects on cognitive and motor development (Grunau 2009, McPherson 2020).

Pain and stress can cause agitation and a variety of autonomic responses, which can be difficult to distinguish from behavioural signs that are not evoked by pain. While pain may be stressful, stress may or may not be painful. Hence when treating pain, especially prolonged pain, consideration for concomitant environmental modification, support and sedation should be given.

A consistent definition of prolonged pain in neonates has not yet been developed but should be considered to optimise measurement and treatment of prolonged pain (Bretton-Piette 2024). A recently proposed consensus definition has been used to guide the measurement and treatment of prolonged pain in this framework (Ilhan 2022, Bretton-Piette 2024).

Acute episodic pain - is a painful experience in response to a noxious event (e.g. injury or disease) which may (e.g. heel lance) or may not (e.g. intubation or eye examination) be associated with tissue damage. Pain can also arise from medical conditions (e.g. osteogenesis imperfecta) or disease state (e.g. sepsis). This is short-lived and the painful experience often but does not always resolve within a period after the end of the procedure or condition. Moreover, an episode is defined as a single event or a sequence of events related to a procedure (e.g. inserting a central catheter) (Ilhan 2022).

Prolonged pain - whilst lacking a universally agreed definition, generally refers to pain that persists despite treatment, lasts longer than may be expected, is no longer proximate to an event, or a continuing painful disease state and is associated with nervous system changes that may lead to primary and secondary hyperalgesia and allodynia (Anand 2017, Ilhan 2022. Bretton-Piette 2024, Cannavò 2022). A prolonged pain state in the preterm neonate can occur in conditions such as prolonged interventions like mechanical ventilation, inflammatory conditions and in the post operative period.

Principles of Pain Management in Neonates

All neonates whether receiving neonatal intensive care or routine care are exposed to noxious stimuli, out of necessity. Regardless of the circumstances in which a baby is experiencing pain, there are fundamental principles that should guide the measurement and treatment of pain.

Key Principles

1. Neonatal Units should have written, evidence-based guidelines in place.
    a. Standardisation of pain management has been shown to improve outcomes.
    b. Guidelines should be regularly updated in line with new evidence.

2. Despite the significant challenges associated with the measurement of pain, available validated tools should be used consistently to assess pain on a continuing basis throughout hospitalisation.
    a. Potentially useful pain assessment tools are highlighted in the Pain assessment section.
    b. Different tools may be appropriate for different situations and for the assessment of acute episodic pain or prolonged (chronic/persistent) pain.

3. Unnecessary invasive painful procedures should be avoided (Hall 2014).
    a. Rationalise the use of 'routine' blood tests unless required to guide clinical management.
    b. Consider whether invasive procedures are necessary and whether the results of investigations will be acted upon.
    c. Use alternatives to blood tests e.g. use of transcutaneous tools e.g. CO_2 and bilirubin monitoring.

4. Health care professionals should be aware that not all signs of distress indicate pain.
    a. Neonates have a limited behavioural repertoire, and it can be challenging to determine the origin of distress, especially when ventilation, sedation or muscle relaxation. complicate the clinical picture.
    b. Simple needs such as hunger and or wet nappy, and responses to positional discomfort or intrusive external devices may present in a similar way to pain.
    c. An unsettled neonate may be showing signs of inappropriate/ineffective ventilation.

5. A multimodal tiered approach should be used to treat neonatal pain (Table 1).

6. Developmental care strategies should be implemented in pain management.
    a. The importance of parents as part of the care giving team should be recognised. They should be involved in their child's care from the beginning.

7. A combination of non-pharmacological approaches should be used consistently to promote comfort and to support babies during painful procedures.

8. Potential benefits and risks should be balanced when using pharmacological treatments, which should be used judiciously to improve effectiveness and minimise tolerance and adverse effects.

Table 1: Multimodal tiered approach to manage neonatal pain

Step 1	Parental involvement: skin-skin care, modification of the sensory environment Plan the timing of the procedures with parents and consider including it in care plan Avoid painful procedures and unnecessary handling Optimise procedure: venepuncture vs heel prick, use of transcutaneous tools e.g. CO2 and bilirubin monitoring Avoid multiple painful procedures on the same day (e.g. ROP screen and immunisation)	**Regular pain measurement with validated tools**
Step 2	Plan care giving activities/procedures to allow recovery and rest Non-pharmacological interventions: skin to skin care, facilitated tucking/ swaddling, non-nutritive sucking, breast feeding or expressed breast milk (sucrose if EBM not available) Pre-emptive use of non-pharmacological interventions and short acting analgesia prior to procedures, considering the severity gradation	
Step 3	Paracetamol: Intravenous or Oral	
Step 4	Opioids (lowest dose for shortest period) If prolonged use of Opioids- alpha-2 agonist (consideration for gestational age needed)	
Step 5	Local anaesthetic where applicable by subcutaneous lidocaine or local application	
Step 6	General anaesthesia or deep sedation	

Communicating with parents in painful procedures

The positive effects of parental presence in reducing pain and stress are well documented (Vinall 2013, Milgram 2010, Jones 2018). Health care professionals should work with parents to ensure that all steps are taken to minimise their baby's exposure to pain. It is important to ensure that information about pain and comfort is provided to parents (Ullsten 2021).

Parents should be

a) ***Informed*** about the event and potential side-effects. These side-effects include pain and an explanation of how pain relief would be provided (BLISS UK).

b) ***Enabled*** to make informed choices about how they would like to be involved in their baby's treatment and care. The information about pain should be objective, and our natural tendency to downplay the existence of pain should be avoided (Seers 2018). Talking about pain especially in neonates, is highly sensitive and needs to be done compassionately, using words that parents understand, at a time when parents can be receptive to the information.

c) ***Offered*** the opportunity to be with their baby when undergoing painful procedures where possible. Whilst some parents may not be able to be present during procedures, it is important that they are told that procedures are happening so that they can make an informed choice. There should be an ongoing discussion with parents throughout their baby's stay on NICU and the bedside care plans should embed planning of non-emergent procedure.

d) ***Encouraged*** to be present during medical procedures. Parents need confidence to handle their baby, and need to be reassured, taught and encouraged to provide comfort during or after medical procedures and when their baby experiences pain due to their medical conditions. Parents should be given an option every time procedure is scheduled as circumstances/feelings may change.

e) ***Involved*** in techniques such as hand-holding and steady touch (which can be introduced early) and skin-to-skin care. Parents need to be told how their presence, voice and touch can comfort their baby when they experience pain.

f) ***Provided*** with accessible information guides at the point of care (example Appendix A) to ease communication and enable parents to ask informed questions.

g) ***Reassured*** that if they are unable to be present, health care professionals would aim to provide comfort measures during procedures.

Table 2: Communication of information to parents around painful procedures (BLISS UK)

What?	What procedure is happening?	Explain the procedure in simple language and acknowledge if it is likely to cause pain.
Why?	Why is the procedure needed What is the expected outcome?	Explain why the procedure is happening
How?	How can parents be involved, if they want to be, and what are the benefits?	Explain that parental presence can increase comfort. Teach parents how they can be involved in their baby's care in advance of procedures.
When?	When is the procedure expected to happen?	Parents can choose if they want to be there, but even when not present, it is important that they know what is happening. Avoid terms that may influence their decision such as "you don't want to see this".
Questions	Give parents the opportunity to ask questions.	Parents can describe their concerns and communicate their preferences.

Neonatal units should facilitate regular education and training of staff to enhance parental involvement in management of their baby's pain. A consideration of language, mental health and neurodiversity would be needed during these communications.

Pain assessment

Pain assessment is essential to achieve optimal pain management. The subjective and complex nature of pain makes pain assessment challenging. A multi-dimensional approach to pain assessment is recommended (Eriksson 2019).

- A validated pain assessment tools/scale should be used to evaluate neonatal pain, and appropriate interventions should be implemented.
- The pain assessment scores should be included in the bedside observation chart to enable regular review.
- It is imperative to train staff to use the assessment tools which have been adopted by a NICU to improve clinical utility (Fortney 2020).
- The expected pain of a procedure should always be anticipated so that measures can be put in place (Appendix A) rather than only using a retrospective score.

Pain assessment tools

Painful procedures elicit a range of behavioural, physiological (Appendix B), and neurophysiological responses. Neonatal pain assessment tools are comprised of one or several measures: physiological, behavioural and contextual.

a. *Physiological measures* include heart rate, respiratory rate, oxygen saturation and blood pressure. They do not always correlate with other measures of pain as they are influenced by contextual factors (level of consciousness, prematurity, medications, anxiety, stress, fear and temperature). These may be the only reliable indices in a baby who is muscle relaxed, neurologically impaired and/or critically ill.
b. *Behavioural measures* include facial expressions, crying, extremity movement and tone, irritability and sleep.
c. *Contextual measures* include sleep state and gestational age of the infant.

When using clinical scoring systems to assess pain, it is important to know the circumstances when a tool is valid for use. Most tools incorporate behavioural and physiological measures and adjust the pain scores based on contextual factors such as gestational age.

There is no specific pain assessment tool that is consistently used across all NICU settings. Some commonly used pain assessment tools which are validated for both term and preterm neonates are shown in Table 3. None comprehensively addresses all areas needed to reliably identify and treat neonatal pain in all circumstances. They are also not validated for post-operative pain assessment.

Overall, the N-PASS tool scores the best on all criteria (Llerena 2023). The PIPP and PIPP-R have been used extensively in pain research (Stevens 2010) but include assessment of facial expression from videos and can be challenging to use in the day-to-day clinical setting.

Table 3: Neonatal Pain Assessment Scales (Llerena 2023, Giordano 2019)

Pain measures	Age cut off	Continuous Pain	Acute Pain	Chronic Pain	High Interrater Reliability	Distinguish between pain and stress	Indicators
Neonatal Pain, Agitation and Sedation Scale (N-PASS)	≥23 weeks	+	+	+	+	+	Five items include behavioural state and physiological parameters
Comfort Assessment Neo Scale (COMFORTneo)	≥24 weeks	+	+	+	X	+	Seven behavioural dimensions
Premature Infant Pain Profile- Revised (PIPP-R)	≥26 weeks	o	+	+	X	+	Two physiological , Three behavioural Two contextual Items
Neonatal Infant Pain Scale (NIPS)	≥27 weeks	X	+	X	o	+	Six behavioural indicators

(+) factor included, (X) factor excluded, (0) Further investigation needed

The Astrid Lindgren Children's Hospital Pain Scale (ALPS-Neo) scores can be used for continuous pain assessment in neonates. It consists of five behavioural items and is suitable for babies from 23 weeks' gestation. It is primarily a tool for ensuring continuous comfort and developmentally appropriate care of babies in NICU. It has proven easy to implement and user-friendly, permitting fast, reliable observations with high inter-rater reliability (Lundqvist 2014).

For the assessment of post-operative pain, the following scales are validated in preterm and term populations (Llerena 2023).

a. Multidimensional Assessment of Pain Scale (MAPS)
b. Pain Assessment Tools (PAT)
c. Children and Infants Postoperative Pain Scale (CHIPPS)

Special consideration should be given to the following situations when applying pain scoring tools:

- Preterm neonates have hypersensitivity to sensory stimuli. This may be documented by an exaggerated response to procedures that are not generally painful such moving, handling e.g. nappy changes.
- Neonates with neurological impairment may exhibit altered processing and modulation of pain. These patients may not display the usual behavioural and physiological responses to pain.
- Neonates who are withdrawing from opioids or maternal substance use, may exhibit behaviours that resemble pain responses, but are not in response to a noxious stimulus.

Frequency of Pain assessment

Frequency of pain assessment depends on the clinical situation. If pain is a concern, then the frequency of scoring should be increased.

Table 4: Suggested frequency of pain assessment in different situations

Situation	Frequency
Receiving mechanical ventilation Has central/peripheral intravenous lines and feeding tubes	4-6 hourly (Bretton-Piette 2024)
Diagnostic and therapeutic procedures	During and after procedure to monitor the effectiveness of pain relief interventions
Receiving scheduled or continuous analgesic infusion	4-hourly
Receiving regular analgesics but required PRN dose or has a dose change of continuous analgesic infusion	1 hour after analgesic dose to establish effectiveness
Post-operative	Immediately after operative procedures Hourly until analgesia optimised Thereafter 4-hourly until off medication, then resume routine assessments
Long term ventilated neonates	At least one pain scores on every shift

Pain score and timing along with any intervention and effectiveness should be documented in the patient medical records. This is facilitated by embedding the pain score in the regular observation charts. Any special considerations to be taken into account when completing the scores should be documented and handed over to the next shift to ensure consistency in pain assessment.

Management of Acute Procedural Pain

Health care professionals should anticipate the severity of pain likely to be associated with a particular procedure and implement non-pharmacological and pharmacological strategies prior to commencing procedure (Laudiano-Dray 2020). This is preferable to reacting only to post procedural pain.

Table 5: Strategy to manage acute episodic pain

Pain Severity	Strategies
Mild	Non-pharmacological measures
Mild to Moderate	Non-pharmacological measures
Moderate	Non-pharmacological but consider pharmacological where appropriate
Severe	Both non-pharmacological and pharmacological
Extremely severe	Both non-pharmacological and pharmacological, including topical analgesia

Table 6: Management of acute episodic pain during neonatal procedures

Procedure	Non-pharmacological measures	Pharmacological options
Eye drops instillation	Apply combinations of non-pharmacological measures using four-handed technique (the second person ideally is the parent or a second health care professionals) Support & involve parents actively Protect from direct light, loud and mechanical sounds Skin to Skin care (full chest-to-chest Kangaroo care) for preterm babies or Breastfeeding for term babies Facilitated tucking and/or swaddling Non-nutritive sucking Expressed breast milk or Sucrose Avoid cluster care and allow recovery	
Orogastric tube insertion		
Nasal prongs insertion for CPAP		
Urethral catheterisation		
Heel lance		
Adhesive Tape removal		Solvent Swab Adhesive Remover (APEEL)
Naso/oropharyngeal suction		
Venepuncture/ cannulation*		Topical anaesthetic- Lidocaine cream (LMX-4) for neonates over 1month CGA with intact skin
Central line placement		Consider opioid bolus if ventilated
Endotracheal suction		Use appropriate suction pressure Choose appropriate catheter size and length (suction should only be to the tip of the ETT and should never exceed more than 0.5cm beyond the tip of the ETT)
Intramuscular injection		Post procedure – IV/PO Paracetamol (if needed)
Peripheral arterial puncture		
Painful wound dressings		If ventilated- IV fentanyl bolus If not ventilated- consider IV/Oral Paracetamol
ROP examination		Pre-procedure- Paracetamol (if needed) Post procedure Modulate environment- eye pads, minimal light exposure

			Paracetamol if not ventilated Opioids if mechanically ventilated (use sparingly) (Thirunavukarasu 2022)
	ROP Bevacizumab intravitreal injection		Pre-procedure If not ventilated- Oral/IV Paracetamol +/- Chloral hydrate If mechanically ventilated- IV fentanyl (Miller 2018) Topical anaesthetic (to be used cautiously & sparingly)
	ROP laser treatment		Mechanical ventilation + laser room Opioids +/- Muscle relaxants
	Lumbar puncture		Topical anaesthetic- Lidocaine cream (LMX-4) for neonates over 1-month CGA with intact skin (Pessano et al 2023) If mechanically ventilated- opioids bolus can be considered
	Chest drain placement and removal		*For insertion-* 1% lidocaine local subcutaneous infiltration IV bolus of Paracetamol If ventilated – consider IV bolus of opioids *Whilst chest drain in situ –* If high pain scores- consider administering regular paracetamol Ensure chest drain is not mobile at point of insertion (as can lead to constant skin rubbing)
	Extravasation injury		Local Anaesthetic- Hyaluronidase + Analgesia (Paracetamol +/- Opioids) After procedure- Regular analgesia (paracetamol) initially, and then as and when needed
	Fractures and Injuries	Specific measures Handle and position carefully Positioning, splinting and comfort measures with advice from orthopaedic surgeons and physiotherapists	Regular analgesic should be given for the first 24-48 hours, Subsequently the dosing can be given as needed, and before procedures.

Pain scores should be continuously measured to allow escalation or de-escalation of treatment as necessary.

Pain management during Therapeutic Hypothermia (TH)

The appropriate use of analgosedation is important to provide comfort and to prevent stress and shivering during therapeutic hypothermia. Preventing stress can be seen as a component to limit further injury in vulnerable brain (McPherson 2020). However, it is also important to recognize that medications have the potential to profoundly alter the developing brain in critically ill encephalopathic neonates

1. Infants undergoing therapeutic hypothermia treatment may not be able to display typical behavioural signs of pain and physiological parameters may also be altered.
2. There have not been clinical trials to determine the most appropriate analgosedative or the regimen (repeated boluses or continuous infusion). Type of analgosedative can be guided according to the unit first line choice.

3. Clinicians should be aware of the altered pharmacokinetics and pharmacodynamics of analgosedation during hypothermia and the need for careful titration (Zanelli S 2011).
4. Mild to moderate hypothermia decreases the systemic clearance of cytochrome metabolised drugs (opioids and midazolam) during TH.
5. Intravenous boluses of opioids (fentanyl or morphine) instead of continuous infusion can help to reduce the risk of high cumulative doses of opioids.
6. If continuous infusion is used, the lowest dose of opioid should be given for the shortest possible time (Favié 2019, Frymoyer 2017).
7. Further studies are needed to explore efficacy of other analgosedative drugs such as Dexmedetomidine, which may also be neuroprotective, beside opioids (Baserga 2021).

Postoperative Pain Management

Adequate pain control in the post-operative period is essential to minimize endocrine and metabolic responses to surgical pain and has been shown to significantly improve outcomes, such as recovery time and healing. It has also been shown to prevent the development of prolonged pain (Furdon 1998). Each neonate responds to both pain and medications differently. Clinical judgement, pain scoring, gestational age, underlying diagnosis, previous exposure to opioids/sedatives and type of surgical procedure needs to be considered in managing post-operative pain.

Neonates are benefitted from ***enhanced recovery after surgery (ERAS) pathways***. This includes delivery of standardised, evidence-based collaborative care throughout the surgical journey including the intraoperative and post-operative periods. The pathways include interventions in areas such as antibiotic use, fluid management, temperature homeostasis and pain management (Brindle ME 2020).

Although neonates vary in their individual responses to pain, surgical procedures can be classified as **POTENTIALLY** causing mild, moderate or severe pain depending on the level and location of tissue injury. Expected severity of pain can be discussed in the ERAS communication.

Key principles for post-operative pain management

1. Regular pain assessment should be done using a validated tool
2. Use of an opioid sparing, multimodal analgesia is recommended
3. The lowest dose of opioid should be given for the shortest possible time
4. Regular paracetamol and regional anaesthesia to reduce the exposure of neonates to opioids and other anaesthetic agents
5. Morphine is the pharmacological agent recommended for post-operative pain management
6. Neonates <7 days require significantly less morphine postoperatively than older neonates (Bouwmeester 2003)
7. Fentanyl use is indicated for moderate to severe procedural pain and reserved for post-operative pain management when morphine dose has increased to a high dose and pain remains severe
8. Fentanyl can be considered as a first line post-operative pain management agent for neonates with hypotension or if there is any concern of hypotension developing
9. If fentanyl is used as a continuous infusion, consider starting at a low dose and titrating in small increments according to response
10. If 2 consecutive pain scores indicate no pain or oversedation, titrate the opioid dose based on duration of exposure.

Table 7: Classification of surgical procedure according to expected severity pain and management (Sick Kids Hospital, Canada Guideline 2020)

Pain Severity	Procedures	Management
Mild Pain	Minimally invasive procedures (e.g. bronchoscopy, laparoscopic surgeries) Myelomeningocele repair Patent ductus arteriosus device closure Colostomy creation Uncomplicated inguinal hernia repair Gastroschisis patch repair with no previous silo (primary repair)	▪ Use non-pharmacological measures ▪ Scheduled paracetamol for 48 hrs (IV or Oral) (Ceelie, 2013; Antti Harma, 2016) ▪ Assess pain regularly using validated tool ▪ Intermittent IV morphine bolus for breakthrough pain ▪ If pain scores indicate moderate/severe pain, give morphine bolus, commence low dose morphine continuous infusion and titrate according to pain scores.
Moderate pain	Abdominal drain insertion Tracheostomy/critical airway procedure Incarcerated hernia repair Gastrostomy tube insertion Omphalocele (small) Gastroschisis closure (uncomplicated) Gastroschisis silo insertion	▪ Use non-pharmacological measures ▪ Scheduled IV paracetamol for 48 hrs ▪ Commence low dose continuous IV morphine ▪ Intermittent IV morphine bolus should be prescribed as PRN for breakthrough pain If on opioids 24 hours prior to operation ▪ Continue infusion but increase by 10% from pre-operative dose ▪ If operative analgesic requirements are high, an increase >10% from pre-op dose may be required Assess pain regularly using a validated tool and titrate analgesic dose up or down ▪ If pain management is escalated multiple times or morphine is at a maximum dose and not providing adequate analgesia, then consider switching to an alternative opioid (e.g. fentanyl)
Severe Pain	Congenital diaphragmatic hernia (CDH) repair Oesophageal atresia and tracheoesophageal repair Patent ductus arteriosus ligation Thoracotomy Laparotomy (excludes colostomy creation) Surgical necrotizing enterocolitis Gastroschisis or omphalocele closure under tension	▪ Use non-pharmacological measures ▪ Scheduled IV paracetamol for 48 hrs ▪ Commence IV morphine low dose morphine ▪ Intermittent IV morphine bolus should be prescribed PRN for breakthrough pain If on opioids 24 hours prior to operation ▪ Continue infusion but increase by 10% from pre-operative dose ▪ If operative analgesic requirements are high, an increase >10% from pre-op dose may be required Assess pain regularly using validated tool and titrate analgesic dose up or down ▪ If pain management escalated multiple times or morphine is at maximum dose and not providing adequate analgesia, then consider switching to an alternative opioid (e.g. fentanyl) ** ▪ For adjunct sedation, consider addition of alpha 2 agonist or benzodiazepine (with consideration of gestational age)

**Consider the difficulty of the procedure/surgery. If pain is more than expected consider other factors e.g. medical device, extravasation.

Management of prolonged pain

Many of the symptoms of prolonged pain are similar to those of agitation, or of an underlying disease state, particularly in neonates with bronchopulmonary dysplasia or cardiac conditions. The difficulty in delineating pain versus agitation additionally makes application of assessment tools and management challenging.

General principles

A standardised assessment tool to assess prolonged (chronic pain) should be adopted by the neonatal unit. A multimodal, individualised approach consisting of both non-pharmacological and pharmacological management of pain and sedation is considered ideal (Donato 2019).

Management of preterm neonates during invasive mechanical ventilation

The optimal approach to preterm neonates experiencing prolonged pain and agitation during invasive mechanical ventilation remains unclear. These principles can be applied

1. During mechanical ventilation, neonatal stress should be minimised by using a combination of non-pharmacological measures individualised to the neonate
    a. Nursing care: Consideration should be given to the type, frequency, and intensity of nursing care provided to preterm neonates with prolonged pain. Care delivery should be adjusted to decrease stress exposure.
    b. Parental interaction: A focus on increasing parental interaction can buffer and reduce the extent to which stressful experiences become biologically embedded (Gao 2015) and improve physiological stability (Chi 2016). Parental presence, with a familiar voice and odour is the most important aspect of non-pharmacological support for babies with prolonged pain or discomfort.
    c. Other non-pharmacological measures (as detailed in Non-pharmacological management section) should be adapted.

2. Before escalation to pharmacological treatment, ensure that agitation and discomfort are not a result of inadequate ventilation or ventilator asynchrony.
3. Currently controversy exists regarding the role of continuous analgesia or sedation in preterm neonates requiring prolonged mechanical ventilation who exhibit agitation refractory to non-pharmacological therapy.
4. Pharmacological treatment with opioids should be used extremely cautiously in mechanically ventilated preterm neonates born at 22 -27 weeks' gestation in the first two weeks of life (Ancora 2019).
5. In the first two weeks of life, preterm neonates have high sensitivity to morphine, hence only a low dose of continuous infusion should be used if needed.
6. Continuous sedation using pharmacological treatment should be avoided in preterm neonates undergoing short durations of invasive mechanical ventilation. Intermittent slow boluses of opioids are recommended, as required, based on pain scores and before invasive procedures (Ancora 2019).
7. Continuous infusions of opioids should be used in neonates with severe respiratory failure due to surgical diseases, malformations, severe sepsis, pulmonary hypertension and neurological diseases, as they might require frequent boluses of opioids to maintain adequate analgesia (Anand 2004, Lago 1998, Simons 2003).
8. Neonates should be given high initial opioid doses to reach a rapid analgesic effect by reaching therapeutic drug levels rapidly. The infusion should be decreased as soon as possible to the lowest effective dosage, based on pain scores. This approach reduces the cumulative dose of

opioids and decreases the risk of tolerance (Anand 2007, Anand 2010).

9. If continuous infusion or nonpharmacological analgesia are inadequate, additional boluses of opioids (same opioid as used for the continuous infusion) should be administered before painful invasive or skin breaking procedures,
10. In cases where long-term treatments are required, when the existing opioid can no longer effectively control the pain, even at the maximum recommended dose, then rotate the opioids (Anand 2010).
11. Standardised pain assessment should always be used to titrate the dose of opioids, as weaning to a lower dose for even a short period is helpful in delaying tolerance.
12. Where other analgosedative treatments have proved ineffective and opioid sparing is desirable, a continuous intravenous infusion of alpha-2 agonist (clonidine/ dexmedetomidine) can be considered (Amigoni 2022). Gestational age consideration is important. There is limited evidence to support the use of alpha-2 agonists (dexmedetomidine and clonidine) as long-term data is currently not available. These drugs are known to have sedative effects and good tolerance without significant adverse effects (Chrysostomou 2014).
13. Midazolam infusions are not recommended for preterm neonates because of the increased incidence of adverse neurological events (Ng 2012, Duerden 2016).
14. It is not necessary to discontinue opioids after prolonged therapy in neonates extubated with non-invasive ventilation, if they are on low dosing and breathing spontaneously as the respiratory depression effect of the opioids usually resolves as tolerance develops.

The implementation of a standard protocol promoting judicious use of analgosedatives has been found to decrease exposure to these medications which can show a reduction in the development of tolerance and refractory pain and agitation (Neunhoeffer 2017).

Management of term neonates during invasive mechanical ventilation

1. The same principles as those described for preterm neonates apply to term neonates during invasive mechanical ventilation.
2. A focus on non-pharmacological measures is important.
3. Analgesia and sedation should be optimised using opioids and, if necessary, with the addition of alpha- 2 agonists.
4. In some cases where optimal sedation is not achieved for example, in cases of pulmonary hypertension, severe air leaks or major surgery, the use of midazolam in association with opioids for short period can be considered if the baby is not hypotensive.
5. Doses of midazolam should be individualised based on postconceptional age and the treatment and should be limited to a few days (Smith 2022).
6. Clearance of midazolam is reduced by concomitant treatment with opioids; hence midazolam should be used at lower dosages when used with opioids (Smith 2022).
7. Due to the negative effect of benzodiazepines on neurodevelopment in patients less than 3 years of age, along with the direct, dose-dependent association with the development of delirium, benzodiazepines are recommended as a third line for sedation and should not be used for prolonged periods.

Refractory pain

This can be defined as the need for more than three analgosedative drugs, the presence of inadequate sedation that lasts more than two hours, the need to increase doses to higher than the 90th percentile from the usual starting dose, or the need to administer neuromuscular- blocking agents to improve ventilator asynchrony (Amigoni 2022, Oschman 2024).

A component of refractory pain may be attributable to the development of hyperalgesia and managed according to guidance in the Managing tolerance and hyperalgesia section.

Non-pharmacological management

Developmental care practices minimise the effects of pain and relieve discomfort (Montirosso 2016).

Environment modulations

The mismatch between the intrauterine and extrauterine environments is stressful for preterm or sick neonates. Creating a calm environment for the baby and their family helps to minimise hypo or hyperactivation of the baby's immature autonomic nervous system in regulating stress from environmental triggers, including procedures.

1. Protect sleep
    a. Identify when a baby is asleep. Decide the timing and adaption of procedures to protect their sleep.
    b. Protect from direct light and loud or mechanical sounds.
    c. Insulate the incubator with cot covers to limit sound exposure from monitors and alarms
    d. Remove unnecessary conversations from the nursery environment especially during painful procedures (White, 2013).
2. Provide physical support
    a. A supportive containment strategy replicates the spatial limitations of the womb (Altemier 2013).
    b. Therapeutic positioning is fundamental in supporting a baby to be comfortable and physiologically stabile. Correct positioning can minimise stress and pain, protect sleep, and provide a nurturing sensory and social environment.
    c. Support self-regulation by providing age-appropriate boundaries and midline positioning with hands towards mouth to self soothe.
    d. Prepare the baby's position to reduce additional handling.
    e. Use adjuncts such as comfort squares containing colostrum/ expressed milk or a knitted octopus.

Pacing

a. Observe the baby's behavioural state before starting the procedure for a few moments and provide relationship-based care (Kleberg 2008).
b. Avoid clustering cares, where several caregiving and medical procedures are done at the same time. This heightens stress and does not provide time for recovery.
c. Allow an hour between procedures whenever possible to achieve a sufficient recovery period and a partial or complete sleep cycle (Holsti 2005. Holsti 2006).
d. Allow at least 15 minutes of stability after a transfer (e.g. cot-to-parent transfer) before starting the procedure.
e. Avoid the first 30 minutes post-feed to reduce reflux.

Skin to Skin (Kangaroo care)

a. Is an effective intervention when performing a single painful procedure (Johnson 2017).
b. Has a positive effect on physiological stabilisation and long-term cognitive development (Cong 2009, Ludington- Hoe 2004, McCain 2005, Feldman 2003, Feldmann 2014).
c. Is more effective than holding a baby clothed. (Jones 2021).
d. Is enhanced as an analgesic when combined with breast feeding (Obeidat 2015) and/or feeding with expressed breast milk (Sahoo 2013).
e. Is more effective in relieving pain than sucrose solutions (Sen 2020).
f. Has shown potential effectiveness in improving neurodevelopmental outcomes (Lazarus 2024, Gao 2023) when combined with non-pharmacological measures, such as swaddling and non-nutritive sucking to reduce acute procedural pain.

Encourage the parent/carer to talk to their baby for as long as possible. This is an important measure to maximise comfort, calm the baby, and promote autonomic stability and allows the parent to respond to the baby's cues and needs. If the parent prefers to hold their baby clothed, they should not be discouraged.

Breastfeeding and expressed breast milk

a. Breastfeeding or supplemental breast milk may reduce pain in neonates undergoing painful procedures compared to no intervention/positioning/holding or placebo or non-pharmacological interventions (Boroumandfar 2013, Shah 2023).
b. Breast feeding is known to decrease behavioural and physiological signs of stress in response to painful procedures and can be used as non-pharmacological analgesia (Weissman 2009, Cignacco 2008).

Non-nutritive sucking

Non-nutritive sucking reduces pain in both full-term and preterm neonates (Pillai-Riddell 2023). It is recommended as a non-pharmacological intervention especially if combined with a sweet tasting substance (preferably breast milk, but also sucrose).

Four handed cares

Best practice involves parent/carer if possible or a second member of staff to help the baby cope with cares and stressful procedures. The second caregiver, ideally the parent, provides support to the baby during the procedure. This also ensures that the baby is offered non-pharmacological stress and pain management techniques while the primary caregiver is completing the task.

It is especially desirable in the following groups of neonates:

a. Intubated neonates.
b. Preterm born under 30 weeks in the first 72 hours of life.
c. Neonates with chest drains or additional medical/surgical needs.

Image 1: Four handed cares

Facilitated tucking

Facilitated tucking can optimise physiological stability and reduce pain and stress (Neto 2020). Support the baby with:

a. Shoulders rounded forwards with hands to their face, avoiding the shoulders in a stretched back position**.** Spine in a neutral midline position.
b. Hips to the midline with feet tucked well into the nest; avoiding the `valgus' (turned out) posture in feet and widely abducted hips (frog like position).
c. The head and neck should be in one line, avoiding hyperextension and excessive rotation.
d. The trunk should be supported in a flexed position – avoid stretched out position of arms and legs.

Massage

a. Massage is deemed superior to positive touch and may positively impact pain relief in neonates in same way as kangaroo care and oral sucrose (Field 2011, Yildizdas 2023).
b. It has a high safety profile and is championed by parents (Fitri 2021). There is, however, limited high-quality evidence to support or oppose its routine use for neonates and it is not advisable for extremely preterm neonates.
c. Maternally administered massage or simple touch may moderate the relationship between neonatal stress exposure and the physiologic stress responses (Asadollahi 2016).
d. Further research studies are recommended to inform specific massage methods (Lui 2022).

Pharmacological management

Pharmacological agents

Preterm and term neonates have immature inhibitory pathways, and this is thought to result in more extensive and prolonged responses to pain.

The physiological maturity at different gestational ages affects pharmacokinetics of the drugs and their analgesic effects. When using analgosedative, their known direct and indirect adverse pharmacological effects on neuronal injury must be weighed against the clear adverse effects of untreated pain on the developing brain.

General principles for pharmacological management

1. Regular monitoring of pain scores is essential throughout treatment to guide titration of analgosedatives.
2. Regular review of analgosedatives is vital to ensure that doses are titrated/weaned or opioids rotated in a timely manner.
3. Pre-emptive use of analgosedative can be considered in stable neonates as a continuous infusion is discouraged.
4. Use the lowest therapeutic dose of analgesic that is needed to produce the desired degree of analgesia to minimise adverse effects is recommended.
5. Where opioids are used, monitor continuously for ongoing need and reduce/discontinue at the earliest opportunity.
6. Short acting opioids can be used for procedural pain and long-acting opioids for more prolonged pain and sedation.
7. If an additional bolus of opioids is needed for painful procedure in a neonate on continuous opioid infusion, same opioid as used for the continuous infusion should be administered.
8. Reserve pre-emptive use of opioids for situations where pain can reasonably be predicted based on knowledge of the baby's condition (e.g. necrotising enterocolitis, other inflammatory conditions; post - operatively).
9. Avoid routine use of opioids in ventilated preterm neonates especially in first 72 hours (Al-Mouqdad 2020), If unable to avoid use, infuse at the lowest rate possible and review ongoing need regularly (Simons 2003, Bhandari 2005, Steinhorn R, 2015).
10. Consider opioid rotation if therapy is ineffective.
11. To minimise tolerance, convert intravenous analgosedative to oral agents as soon as possible.
12. When transitioning from invasive to non-invasive ventilation, taper opioids slowly and monitor pain by using a validated pain scale. A complete cessation of analgosedative may not be needed if neonate is on low dose and breathing spontaneously as the respiratory depression effect of the opioids usually resolves as tolerance develops.

Table 8: Pharmacological Management

Class	Medication	Route	Effect	Indications
Non - Opioid Analgesic	Paracetamol	Oral Intravenous Rectal	Analgesic	• Procedural and Postoperative Pain • Mild Pain (monotherapy) • Moderate- severe pain- as an adjunct to opioids
Opioids	Morphine	Continuous infusion Oral	Analgosedative	• Moderate to severe acute episodic pain • Treat prolonged pain e.g. mechanical ventilation, post-operative pain • Morphine infusion is favoured in neonates who have undergone abdominal surgery and have risk of increased intra-abdominal pressure (Koehntop 1986) • Fentanyl is preferred in presence of renal failure, hypotension, reduced gastrointestinal motility (Saarenmaa 1999), and gestational age <27 weeks (Hall 2005) • Prolonged use of fentanyl should be avoided
	Fentanyl	Continuous infusion		
Alpha-2 agonists	Clonidine	Continuous infusion Oral	Analgosedative	• Can be used as an opioid sparing adjunct if prolonged opioid therapy or opioid therapy is ineffective
	Dexmedetomidine	Continuous infusion		
NMDA antagonist	Ketamine	Intravenous Oral	Analgesic	• Use cautiously and sparingly in Hyperalgesia
Benzodiazepine	Midazolam	Continuous infusion	Sedation	• As adjunct sedative in term babies for a **short period** where agitation persists despite optimal opioid and alpha-2 agonist therapy • Avoid use in preterm neonates as associated with significant adverse risk profile (McPherson 2021).
Hypnotics	Chloral hydrate*	Oral Rectally	Procedural Sedation	Short term use as sedative adjunct if alternative agents are ineffective or in these situations: • To facilitate weaning of opioids • To limit the use of IV sedative agents (particularly midazolam) • If neonates still agitated but not in pain
Topical & Local Analgesia	Lidocaine	Topical	Procedural analgesia	• Local subcutaneous infiltration with Lidocaine should be used when performing invasive procedures like chest or abdominal drain insertion or extravasation injury. Correct site should be identified before instilling • Ideally the baby should also receive systemic analgesia e.g. paracetamol, morphine • Topical anesthetic cream Lidocaine should be considered for LP in term neonates >1 month of age with intact skin

* The lowest effective dose should be used for the shortest amount of time, prescribed on a PRN basis and the number of doses required should be regularly monitored. (MHRA 2021, NPPG, 2022).

Specific consideration with pharmacological analgesia

The advantages and disadvantages of various pharmacological analgesia have been given in Appendix C.

Alpha-2 agonists

Centrally acting alpha-2 agonists such as clonidine and dexmedetomidine have analgesic, sedative and sympatholytic effects, and are opioid sparing when used as an adjunct (Dersch-Mills 2019). They are routinely used in adult and paediatric practice (Duffett 2012, Chen 2015, Mantz 2011, Pichot 2012, Reardon 2013). Their off-label use has significantly increased in neonatal practice across Europe and the USA (Curtis 2023, Hunseler 2014, Ragnarsson 2016). Currently they are not consistently used in the UK. There is a lack of evidence regarding optimum/adequate dose and long-term outcomes of alpha-2 agonists in preterm neonates.

Dexmedetomidine

a. Highly selective α_2-adrenergic receptor agonist with both sedative and analgesic action
b. A systematic review including 6 studies identified that Dexmedetomidine can be administered safely at specific dosage ranges in neonates without leading to significant adverse events (Portelli 2024) and provided a reduction in the use of opiates and time on the ventilator. However, the studies included were not randomised controlled trials.
c. A multicentre observational cohort study included 384 babies from 22 to 36 weeks gestation (median 34 weeks), showed a trend over time of increasing use of Dexmedetomidine and a decreasing use of opioids. (Curtis 2023).
d. In clinical studies, Dexmedetomidine has been used in preterm and term neonates receiving mechanical ventilation, during short invasive procedures and for post operative pain control (O'Mara 2012, Curtis 2023, Portelli 2024, Sellas 2019). Currently high-quality evidence from randomised control trials is lacking.
e. The DEXmedetomedine Trial of Adjunct Treatment with Morphine (DEXTA), a three-arm, multicentre, blinded, randomised placebo-controlled trial will commence recruitment of <32 weeks' gestational age in the UK in 2025 (NIHR158535).

Dexmedetomidine can be considered alongside opioids as an opioid sparing adjunct if opioid therapy is ineffective or neonates have been on prolonged opioid therapy. With judicious use of opioids and opioid rotation, its addition would be needed only after 4-6 weeks of prolonged opioid exposure.

Clonidine

a. Clonidine is used in neonates for Neonatal Abstinence Syndrome, weaning opioids and for sedation.
b. In term ventilated neonates Clonidine has been shown to reduce opioid and benzodiazepine demand without substantial side effects (Hunseler 2014).
c. Compared with Dexmedetomidine, Clonidine has a lower selectivity for α2-receptors and as central α2 effects are sedative, clonidine is less sedating (Bada 2015).
d. In a clinical study, Clonidine use has been described in preterm neonates born at between 25-37 weeks' gestation with duration of exposure of 3.8-11.5 days. The subjective effects were positive with few side effects (Ragnarsson 2016).
e. Oral administration in Neonatal Abstinence Syndrome is considered safe and effective for neonates ≥35 weeks (Bada 2024).
f. Current evidence is insufficient to recommend routine use of clonidine as analgosedative in term and preterm neonates receiving mechanical ventilation (Romantsik 2017).

Cautious use can be considered for neonates ≥30 weeks' gestation alongside opioids as an adjunct if

effective analgesia and sedation is difficult to achieve with opioids alone.

Chloral Hydrate

Chloral hydrate is a sedative agent. It has long been considered a useful addition to the sedative options in paediatric and neonatal intensive care, although it is increasingly less frequently used. It has been used in the past to facilitate weaning of opioids, limit use of benzodiazepines and to act as an adjunct to analgosedative if the baby is still agitated. It is used as a rectally administered option where patients have limited intravenous access and can also be given orally.

Extreme caution in neonatal patients is recommended particularly in premature infants as studies have shown that due to immaturity of metabolism, the half-life and incidence of adverse effects are dramatically increased (Wyness 2023).

Following safety update from Medicine and Healthcare products Regulatory Agency (MHRA) in 2021, new prescribing restriction were issued for its use in paediatric patients (MHRA 2021, NPPG, 2022).

- Chloral hydrate should be used only when considered absolutely necessary where alternative enteral agents have been considered, are not appropriate or fail to achieve the desired effect.
- Initiate on a 'when required' basis so that response can be assessed.
- Use the lowest effective dose, frequency and duration possible with frequent review.
- It has been recommended only for short term use (≤ 5 day). Repeated courses are not recommended.

Specific consideration with non-pharmacological analgesia

Sucrose (Lefrak 2006, Campbell 2014, Stevens 2016, Bueno 2023)

a. Effective in reducing behavioural pain response in both preterm and term neonates.
b. The analgesic effect is related to the sweet taste rather than the volume of sucrose administered.
c. Should always be used in conjunction with other non-pharmacological measures such as skin to skin, facilitated tucking, swaddling and non-nutritive sucking.
d. Should not be used to comfort or settle neonates – administration should be confined to neonates who require pain relief associated with procedures.
e. Sucrose should only be used where breast milk is not available.
f. Repeated doses of sucrose should not be used for a single procedure.
g. For maximum effect administer two minutes prior to the painful procedure.
h. The duration of action is 5-10 minutes.
i. ALL doses should be prescribed.

Exclusion criteria as below (Austin 2015)

a. Neonates who are muscle relaxed.
b. Neonates undergoing major procedures and receiving appropriate intravenous analgesia.
c. Neonates with sucrose intolerance.
d. Glucose-Galactose malabsorption.
e. Caution in Neonates with significant respiratory distress, feed intolerance or altered gag/swallow reflex. For these neonates breast milk or sucrose may be applied by swab on anterior part of tongue.

Parents should be advised that sucrose as analgesic is to be used by health care professionals only and should not be used at home.

Weaning analgosedation in neonates

Definitions

Physiological Dependence: Physiological need for an agent to prevent withdrawal symptoms
Iatrogenic Withdrawal: Characteristic pattern of unpleasant signs and symptoms after abrupt cessation or rapid tapering of opioids with CNS depressant effects (Anand 2010).

Table 9: General Principles to consider when weaning analgosedation

Wean one drug at a time
As an adjunct sedative benzodiazepine should be only used for short period therefore can be stopped rather than weaned
Opioids should be weaned first before alpha 2 agonists
Wean stepwise by 20% of the original dose every 24-48hrs and then discontinue
If signs of withdrawal increase, return to the previously tolerated dose and then resume weaning after 48hrs. Alternatively, consider the use of oral clonidine or optimising the dose (if already on this) to manage withdrawal (Bada 2024)
Consider comorbidities of the neonate at the time of weaning

Use appropriate withdrawal assessment tools (Finnegan score or WAT-1 tool) (Frank 2008).

Opioids

Weaning schedules are generally recommended if:

- High doses are required to control pain.
- Initial duration of exposure to opioid medications is more than 5 days.

a) Intravenous therapy (>5 days)
   - Reduce continuous infusion rate by 5 micrograms/kg/hour, and consider weaning every 12-24 hours as tolerated.
   - Convert to oral administration as soon as is feasible. Dosing frequency should be every 4 hrs initially.

b) Oral therapy- weaning as highlighted in ***Table 10*** can be adopted.

Table 10: Weaning requirement based on duration of administration

Duration of opioid exposure	Action
≤ 5 days	Discontinue, weaning not required.
> 5 days	Reduce by 20% of the original dose every 48 hours.
	If not tolerated, step back to previous dose and attempt to wean after 48 hrs. A consideration to weaning by <20% can be given if not tolerated weaning initially
	Once on small weaning dose, extend dosing interval if required

Fentanyl

- Wean IV infusion by 0.5 micrograms/kg/hr every 12 hrs.
- Alternatively, convert to morphine (IV or oral) and follow Morphine weaning plan.

Clonidine

- When used concomitantly, alongside opioids, **wean the opioids first**.
- If clonidine has been used > 2 weeks, wean the infusion rate to 0.6micrograms/kg/hour and then switch to oral (if possible) at 5microgram/kg eight hourly and reduce dose daily by 1 microgram/ kg/dose over 5 days (Phad 2024).
- Abrupt discontinuation may result in symptoms of withdrawal (e.g., agitation, tremor, rapid rise of blood pressure); a gradual reduction of dosage is recommended when therapy is discontinued.

Dexmedetomidine

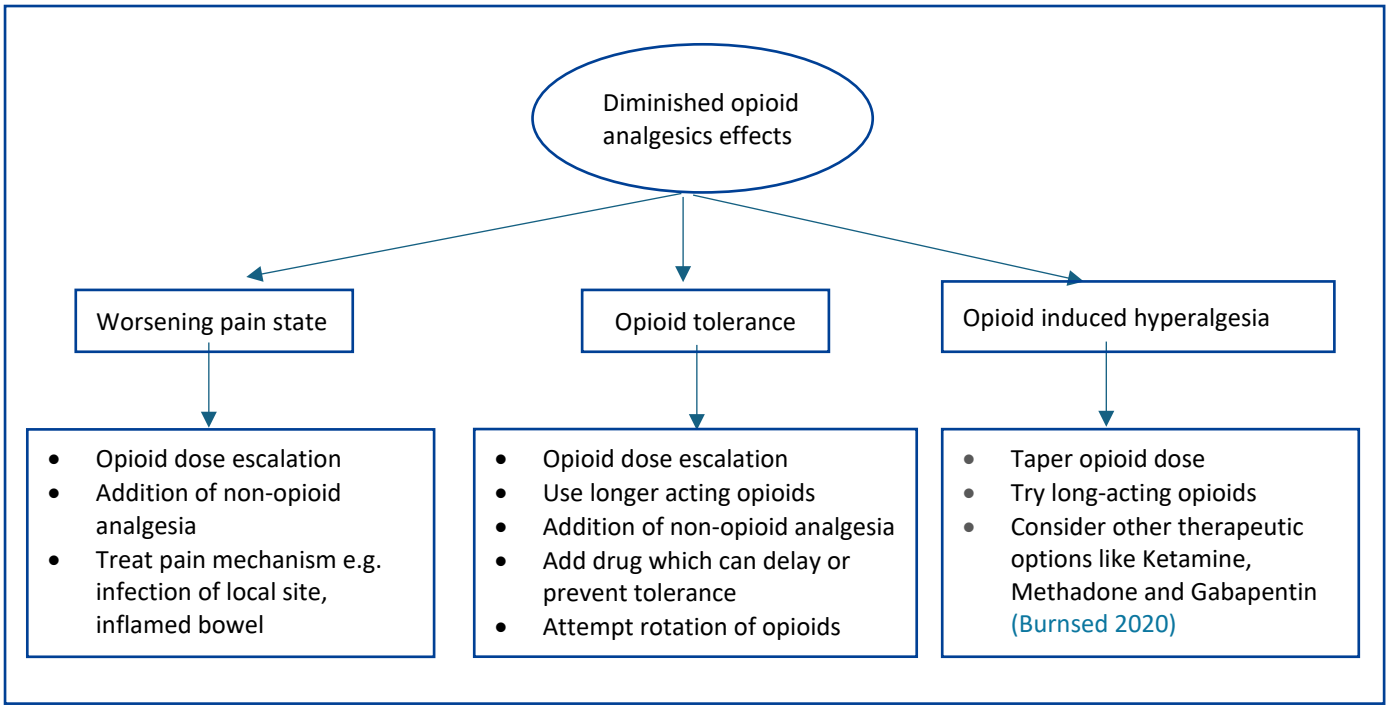
- Infusion should be weaned rather than discontinued abruptly.
- Infusion of ≤24 hours can be ceased abruptly; Infusion >24- ≤ 72 hours: Halve the infusion and then reduce by 0.1 mcg/kg/hour every 12 hours.
- If infusion > 72 hrs- reduce the infusion rate by 0.1 mcg/kg/hour every 12 hours or convert enterally to clonidine. Weaning of continuous dexmedetomidine infusion to half the dose should occur 30 mins after commencement of oral clonidine and complete cessation of infusion after second dose of clonidine (extrapolated from paediatric data Liu 2020).

Managing tolerance and hyperalgesia

Diminished opioid analgesic efficacy or increased opioid requirements can be explained by three distinct clinical possibilities:

1. Worsening pain state.
2. Opioid tolerance.
3. Opioid-induced hyperalgesia (OIH).

Figure 1: Algorithm for diminished opioid analgesics efficacy



Tolerance

Tolerance is defined as decreasing pharmacological effects of a drug after repeated administration or increasing dose requirements of the drug to attain the same clinical effects.

Factors that affect development of opioid tolerance

1. **Duration of therapy**- Opioid tolerance rarely occurs after therapy for less than 72 hours (Anand 1999).
2. **Continuous infusions**: Continuous infusion of opioids induce tolerance more rapidly than intermittent therapy (Hovav 1987).
3. **Gestational Age:** Opioid tolerance develops earlier in preterm versus term newborns (Franck 1989, Anand 1999). The clinical signs of opioid withdrawal, however, are more prominent in term neonates (Doberczak 1991).
4. **Half-life of drugs**- For opioids with short elimination half-life e.g. fentanyl, tolerance and dependence are seen earlier compared to opioids with a longer half-life e.g. morphine (Bot 1998). It also varies based on differing chemical structures (e.g. synthetic opioids >opiates), biological half-lives and interaction with neuronal protein-kinases (e.g. fentanyl > morphine > methadone) (Anand 2010).
5. **Dosage:** Patients receiving lower initial doses are more likely to develop opioid tolerance compared to those receiving high doses. Inadequate analgesia associated with low initial dosing leads to ongoing pain, which require much higher opioid doses to finally regain pain control (Anand 2010).

Strategies to prevent or delay opioid tolerance

A focus strategy to prevent and delay opioid tolerance is essential to allow use of these medications over longer periods. This can be achieved by:

- Adoption of standardised guidelines to manage pain
- Tailoring opioid infusions according to pain assessment scores.
- Administer the minimal effective dose of analgosedatives to reduce tolerance.
- The infusion should be commenced at higher dose to optimise level but titrated down. (recommended). Alternatively, prior to commencing infusion, loading dose of opioids should be given and if response is suboptimal, a slow bolus can be repeated instead of increasing the background infusion dose.
- Consider opioid rotation commencing at an equivalent dose and titrating the infusion to lower doses (e.g. rotating between morphine and fentanyl) (Knotkova 2009).
- To minimise tolerance, convert intravenous opioids to oral agents early.
- Consider adding clonidine or dexmedetomidine to facilitate opioid sparing and delay tolerance, addition in cases of prolonged pain.

Opioid rotation

Opioid rotation refers to switching from one opioid to another to improve the therapeutic response or reduce undesirable effects. It begins with the selection of another opioid at a starting dose that ideally maintains analgesic efficacy. There is limited data to guide opioid rotation in adult patients and this data has been extrapolated to neonates whilst considering the different pharmacokinetic properties of opioids in the neonatal population (McPherson 2020, Fine 2009). The table below illustrates a potential approach to opioid rotation, but this has not been validated within the neonatal population**.**

Table 11: Approach to opioid rotation in the neonate

Current agent	New agent	Dose calculation
Fentanyl	Morphine (microgram/kg/hr)	Multiply fentanyl dose by 20 and reduce by ~25% for cross tolerance
Morphine	Fentanyl (microgram/kg/hr)	If on 20micrograms/kg/hr of morphine switch to 1microgram/kg/hr of fentanyl

If increasing the infusion rate is not having the required effect, consider opioid rotation (e.g. morphine to fentanyl infusion and vice versa). This often occurs after 3-4 weeks and can occur earlier if optimisation to low dosing has not been done.

Switching to oral sedation

Longer duration of opioids will create pharmacological dependence and lead to iatrogenic withdrawal (Dominiguez 2003). Guidance on the optimal timing for transitioning from intravenous to oral sedation remains unclear, however the neonate must be tolerating enteral feeds. Once the decision is made to discontinue intravenous sedation, several oral agents can be considered (Table 12).

Table 12: Intravenous to oral analgesic/sedation conversions (McPherson 2020, Stroedar 2024)

Current intravenous agent	Oral alternative	Dose calculation
Morphine (microgram/kg/hr)	Morphine (microgram/kg/dose)	Calculate the total daily IV morphine dose in micrograms: e.g. Current dose in mcg/kg/hr x working weight (kg) x 24 Multiply this figure by 2 (for bioavailability) to give total daily oral dose Divide this into six equal doses and prescribe 4 hourly in micrograms Stop the IV infusion after the first oral dose
Fentanyl (microgram/kg/hr)	Morphine (microgram/kg/dose)	Calculate the total daily IV fentanyl dose in micrograms: e.g. Current dose in mcg/kg/hr x working weight (kg) x 24 Multiply this figure by 20 (for bioavailability) to give the equivalent dose of oral morphine Then multiply this figure by 2 (for bioavailability) to give total daily oral dose Divide this into six equal doses and prescribe 4 hourly in micrograms Stop the IV infusion after the first oral dose
Dexmedetomidine (microgram/kg/hr)	Clonidine (microgram/kg/dose)	Calculate the total daily IV dexmedetomidine dose in micrograms: e.g. Current dose in mcg/kg/hr x working weight (kg) x 24 Multiply this figure by 0.4 (conversion factor) to give the equivalent total daily dose of oral clonidine. Divide this into three equal doses and prescribe 8 hourly in micrograms
Clonidine (microgram/kg/hr)	Clonidine (microgram/kg/dose)	Wean the intravenous clonidine dose to 0.6micrograms/kg/hour and then switch to oral dosing of 5microgram/kg 8 hourly. OR If the intravenous dose is < 0.6microgram/kg/hour switch to an oral dose of 3microgram/kg 8 hourly If the intravenous rate is between 0.6-1microgram /kg/hour switch to an oral dose of 5microgram/kg 8 hourly If the intravenous dose is > 1microgram/kg/hour switch to an oral dose of 5microgram/kg 8 hourly, if not providing adequate effect consider increasing the dose to 5microgram/kg 6 hourly if neonate is not hypotensive/bradycardic.

Hyperalgesia

Opioid-induced hyperalgesia (OIH) is an apparent paradox, whereby the ongoing or increased administration of an opioid leads to an unexpected state of increased pain perception and sensitivity rather than improving analgesia.

The state is characterised by the development of hyperalgesia and allodynia (pain caused by a stimulus that does not normally elicit pain). This contrasts with tolerance, where increased administration of opioid is required to maintain the same analgesic effect. Opioid-induced hyperalgesia occurs even in the absence of opioid tolerance.

Visceral Hyperalgesia (Edwards 2016) in neonates with neurological impairment can manifest as gastroesophageal reflux, poor weight gain, constipation and feeding intolerance due to poor gut motility, spasticity and pain. These patients may also present with apnoeic episodes, grimacing, inconsolability, restlessness, hypertonia, stiffening, and back arching

There are limited management strategies for OIH, primarily due to the lack of research and the difficulty in diagnosis. (Oschman 2024).

If OIH suspected**:**

a. De-escalation of opioid dose may be helpful (Oschman 2024, Hallett 2012).
b. Opioid rotation has not shown to be effective for OIH or for decreasing opioid exposure (Tompkins 2011).
c. For treating OIH or refractory pain - dexmedetomidine, ketamine (cautious use for short duration), gabapentin (cautious use for short duration) and methadone have been suggested in a variety of sources as potential options in neonates (Tompkins 2011, Amigoni 2022, Hallett 2012).

Future research recommendations

This framework focuses on evidence-based knowledge of how best to measure and treat neonatal pain and rightly does not reflect insights from anecdotal evidence or personal experience. Nevertheless, in preparing these recommendations, members of the working group were able to reflect on available evidence and identify evidence gaps.

Research is needed to optimise the measurement and treatment of neonatal pain (Eccleston 2021), so that we can provide optimal therapies for acute and ongoing pain conditions and best integrate family care into our pain management practices. This is not easy, as the rapid developmental change in neonatal physiology means a one-size-fits-all approach for the treatment of pain is not possible.

At the heart of effective neonatal pain treatment, is the ability to accurately measure pain. Accurate measurement allows treatment effects to be assessed, drugs to be titrated according to need and personalised dosing regimens to be created. Nevertheless, as pain is subjective, pain measurement in non-verbal populations is difficult, and we are reliant on proxy behavioural and physiological observations to subjectively quantify pain. Given pain experience occurs in the brain, new insights about how the immature neonatal brain responds to painful procedures and pathologies will help drive new more accurate pain measurement; especially when techniques such as EEG (Asbury 2024, Jones 2021, Rupawala 2023), Near infra-red spectroscopy (Ranger 2014) and fMRI (Goksan 2015) are combined with other well-described behavioural and physiological observations (Asbury 2024). Ultimately, evidence-based consensus is needed on the best clinically useful pain measurement approach, which will most likely combine developmentally sensitive measurements of behavioural, physiological and cerebral activity (van der Vaart M 2019).

A detailed understanding of how best to measure pain, and insight into how to best quantify the short and long-term impact of neonatal pain and its management, provides a means to assess the efficacy and safety of new and existing pain treatment options. Such approaches enable us to assess the efficacy of pain treatment options by conducting high-quality clinical trials, for example to test the analgesic efficacy and safety of less-well studied drugs, such as Dexmedetomidine. Optimising pain treatments for neonates is complex, but our community has the chance to prioritise research that will enable us to provide the best possible pain treatment.

Appendix A: Parent and staff support tool

Prepare and support babies during painful hospital procedures

Follow this 3-step guide:

1. Prepare
- **Use the chart** below to estimate the pain from procedures
- **Parent or staff to get assistance** from a second person

2. Support
- **Combine ways to support** appropriate for each procedure **before, during, and after** until recovery

3. Protect
- Prepare and support to protect **baby's developing brain**

Prepare		Support				
Common procedures	Estimated pain*	Skin to skin	Swaddle	Milk/ sucrose	Soother**	Medicine
Lumbar puncture (LP)	Severe		✔	✔	✔	✔
Arterial puncture (AP)		✔	✔	✔	✔	✔
Endotracheal intubation (ETT)			✔			✔
Intramuscular injection (IM)		✔	✔	✔	✔	✔
Eye examination (ROP)	Moderate	✔	✔	✔	✔	
Endotracheal suction (ETS)		✔	✔		✔	
Intravenous cannulation (IVS)		✔	✔	✔	✔	
Naso/Oropharyngeal suction (SUC)		✔	✔	✔	✔	
Tape removal (TR)		✔	✔	✔	✔	
Nasogastric tube insertion (NGT)		✔	✔	✔	✔	
Heel lance (HL)		✔	✔	✔	✔	
Urethral catheterisation (UC)	Mild to moderate	✔	✔	✔	✔	
Nasal prongs for CPAP (NPr)		✔	✔	✔	✔	
Orogastric tube insertion (OGT)		✔	✔	✔	✔	
Eye drops instillation (ED)	Mild	✔	✔	✔	✔	

*Babies' pain scores from 59 studies (Laudiano-Dray et al., 2020)

**Disclaimer for parents: The use of soother is for the management of painful procedures in acordance with the Baby-Friendly Hospital Initiative for small, sick and preterm newborns, www.unicef.org.uk

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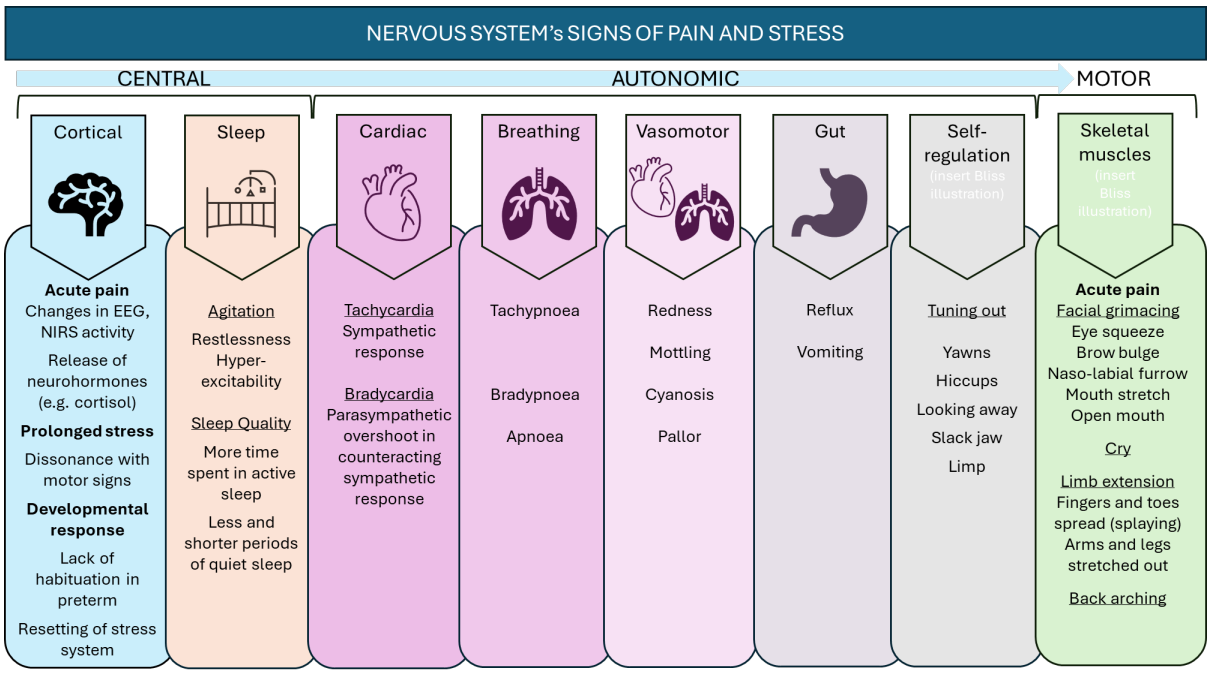
Appendix B: Nervous systems signs of pain and stress



Appendix C: Pharmacological treatment agents

Medications	Advantages	Disadvantages
Paracetamol	• Useful for mild pain as monotherapy • Provides opioid sparing effects	• For moderate/severe pain will require additional analgesia
Morphine	• Use for ≤ 7 days not associated with detrimental long-term neurological effects (McPherson 2021, Anand 2013) • Increased ventilator synchrony	• Hypotension and decreased vascular resistance may occur due to histamine release (Levene 2005) • Use in lower gestation and pre-emptive doses linked with hypotension. Caution advised when using continuous infusion in extremely preterm neonates with pre-existing hypotension (Hall 2005, Hall 2007) • Delayed enteral autonomy (McPherson 2021) • No benefit in long term ventilation (McPherson 2021) • Cumulative exposure linked with neurodevelopmental impairment (McPherson 2021)
Fentanyl	• Rapid onset and shorter duration of action compared with morphine (McPherson 2021) • Decreases heart rate, behavioural pain and neuroendocrine stress responses. • Does not cause histamine release so useful in neonates with pre-existing hypotension and renal impairment (Pacifici 2015) • Less impact on gastrointestinal motility compared to morphine	• Chest wall rigidity may occur when given too rapidly (Anand 2006) • Accumulation significant in preterm/critically unwell neonates (McPherson 2021, Ziesenitz 2018) • Cumulative exposure linked with cerebellar injury and neurodevelopmental impairment (McPherson 2015, McPherson 2021) • Rapid development of tolerance
Clonidine	• Stimulates opioid receptors (Jamadarkhana 2010) • Does NOT cause respiratory depression or gastrointestinal dysmotility (Jamadarkhana 2010, McPherson 2021) • Does not cause oversedation, can reduce opioid requirements and support opioid weaning by reversing noradrenergic activity (Broome 2011, Hunseler 2014, Romantsik 2017) • Oral administration in Neonatal Abstinence has been cited safe and effective (Streetz 2016, Bada 2024)	• Caution in renal impairment as eliminated by kidneys, potential risk of accumulation • Can cause profound hypotension and bradycardia • Risk of rebound hypertension if stopped abruptly
Dexmedetomidine	• Can provide analgesia and augment the activity of opioids (Ojha 2022) • Clinical data suggest superior efficacy compared with opioids (O'Mara	• Limited evidence regarding effects on cerebral activity in preterm neonates

	2012) • Stimulates natural sleep pathway with maintenance of spontaneous breathing and upper airway tone (Ojha 2022) • Renal impairment does not influence the pharmacokinetics to any significant extend • Minimal impact on gastrointestinal motility • Pre-clinical data suggest neuroprotective and anti-inflammatory actions (Mantz 2011)	• Effect on long term outcome not known • May increase the metabolism of caffeine citrate, thereby reducing caffeine's effect
Ketamine	• Potent analgesia, sedation • Rapid onset (1-2 min) • Short duration of action (15-30min) supporting hemodynamic and respiratory stability • Neuroprotective effect in presence of noxious stimuli such as inflammation, pain and stress (Anand 2007, Cheung 2019)	• Neurotoxic effects on immature brain and behavioural outcomes • Negative inotropic effect
Midazolam	• Rapid clearance due to short half-life in older children	• Risk of severe intraventricular haemorrhage, periventricular leukomalacia or death in preterm neonates (Anand 1999) • Decreased cerebral blood flow (Anand 1999, Ng 2012) • Increased doses may result in severe side effects including hypotension, oversedation and myoclonic jerking (De Wildt 2003) • **Benzodiazepines are not recommended in the preterm population**- direct, dose-dependent association with the development of delirium and adverse neurological events like seizures • Clearance delayed in preterm neonates • Fixed body-weight dosing has resulted in considerable differences in plasma concentration levels and sedation levels dependent on gestational age (Voller 2019, de Wildt 2009)
Chloral Hydrate	• Can be administered orally or rectally • Effect apparent within 30 min from administration lasting usually for 4-6 hours	• Cautious use in neonates with hypotension • Cardiac toxicity (ventricular dysrhythmias) and hypotension have been previously reported hence contraindicated in those with severe cardiac disease (Wyness 2023) • Should not be used in patient with hepatic impairment

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