

Clinical Guideline:

Management of babies born to mothers who are on prescribed or misuse medications (opiate and related) leading to drug withdrawal features (Management of Neonatal Abstinence Syndrome (NAS))

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For use in:

EoE Neonatal Units

Guidance specific to the care of neonatal patients.

Used by:

Neonatal Intensive Care Units East of England:

- Medical staff
- Nursing staff
- Paediatric Pharmacist

Key Words:

- Neonatal Abstinence Syndrome (NAS)
- Maternal drug misuse
- Infants of mothers on Methadone Programme
- Infants of mothers on prolonged Opiates use for medical reasons
- Modified Finnegan Score (MFS)
- Medications: Opiates, Morphine; Clonidine; Phenobarbital

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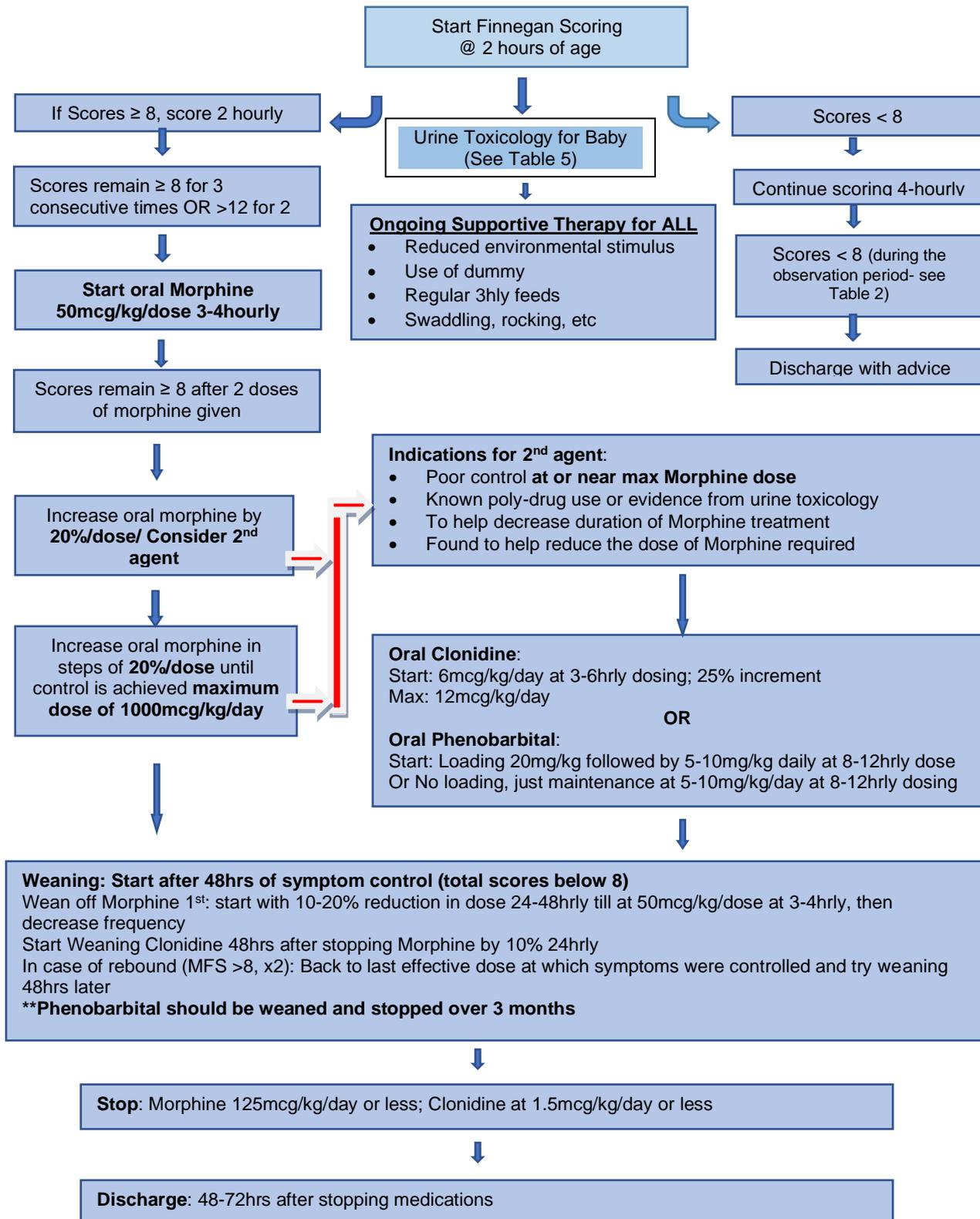
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Summary of Guideline/Pathway



Aims

- To standardise and outline good practice, using best evidence, in the postnatal management of babies whose mothers were known or suspected to have misused drugs during pregnancy or were on medications that may lead to withdrawal features in their babies
- To standardise the care plan between all professionals to meet the needs of the baby and family and ensure communication exists between all professionals, the family and their social support network
- Minimise the impact of withdrawal symptoms for the baby
- Provide appropriate neonatal care for the baby which facilitates maternal / infant bonding
- **The drugs included in this guidance are:** opiates, cocaine, amphetamines, marijuana and poly-drug misuse (from afore mentioned list).
- **The guidance excludes:** management of babies whose mothers were on Mental Health-related medications, such as anti-psychotics and antidepressants (separate guidance under development).

Introduction

Intrauterine exposure during pregnancy, to certain illicit drugs or medications may lead to congenital anomalies and/or foetal growth restriction, increased risk of preterm birth, impaired neurodevelopment and increased rates of neonatal opioid withdrawal known as Neonatal Abstinence Syndrome (NAS), amongst others (**Table 1**).

The exact number of drug-dependent women is unknown because the statistics rely heavily on voluntary patient disclosure. However, there is an increasing trend in the misuse of illicit drugs, as well as in prescribed medication, in pregnant women, nationally and internationally,

The most common and clinically important neonatal withdrawal commonly results from opioid exposure during pregnancy. Among neonates exposed to opioids in utero, withdrawal signs will develop in 55% to 94%. Neonatal withdrawal signs have also been described in infants exposed antenatally to other misused drugs/ maternal medications. (**Table 1**)

In certain cases, signs and symptoms of withdrawal worsen as drug levels decrease (for example, methadone, heroin), whereas signs and symptoms of acute toxicity subsides with drug elimination (cocaine). For most drugs, it is known that the risk and severity of NAS appears to be modified by opioid type and exposure to additional substances, such as maternal smoking and concomitant use of SSRI, sedatives-hypnotics, benzodiazepines, and by the time elapsed between last maternal use and delivery.

However, this guidance does not include the management of babies exposed in-utero to anti-depressants and anti-psychotic medications.

Table 1: Maternal Misused Drugs and/or Medications and Known Outcomes

Drug/Medication	Known outcomes
Alcohol	Acute ingestion: Hyperactivity, tremors for 72 hours followed by lethargy for 48 hours Chronic ingestion: abnormalities include CNS, growth deficiency, facial features, cardiac and musculoskeletal anomalies (Foetal Alcohol Syndrome)
Amphetamines	Increased rate of abruption, IUGR, cardiac anomalies, intracranial lesions including infarcts and haemorrhage; agitation, hyperactivity
Benzodiazepines	'NAS-like' syndrome (neuro-behavioural dysregulation); hypothermia, hyperbilirubinaemia, CNS depression
Cocaine	Acute toxicity in newborn with agitation, tremors, difficulties with feeding, poor sleep; Neurological complications (brain infarcts, haemorrhagic lesions, cystic lesions); higher incidence of prematurity, low birth weight, placental abruption; associated with higher incidence of congenital genitourinary tract and gastrointestinal anomalies- ileal atresia; Short and/or long term neurobehavioral abnormality; limb reduction defects, NEC; myocardial infarction SIDS appear to be more common in cocaine exposed infants
Marijuana	Higher incidence of tremors and altered visual responses No withdrawal effects
Methamphetamines	IUGR, prematurity, placental abruption, foetal distress, adverse long-term neurotoxic effects on behaviour, cognitive skills, and physical dexterity
Opioids (Includes Methadone)	NAS; Preterm labour; Low birth weight/ IUGR; Active/passive detoxification results in foetal distress or foetal loss; sleep deprivation; Increased risk of SIDS; No other adverse outcomes identified so far
Poly-drug use	Increased risk of abnormal pregnancy outcomes, greater risk of SIDS; Increased Infant mortality Rates; Associated with family and social issues

Neonatal Abstinence Syndrome (NAS)/ NAS- like Syndrome

NAS is an array of signs and neuro-behaviours experienced by the newborn that occur after abrupt discontinuation of pregnancy exposure to substances taken by the mother. The term NAS has been principally used to describe neonatal symptoms and signs occurring after prolonged in-utero exposure to opioids such as heroin, methadone, and buprenorphine, and use or misuse of prescription opioid containing medications, such as codeine. However, other substances may produce neuro-behavioural dysregulation in the neonatal period consistent with an abstinence/ withdrawal syndrome, including

benzodiazepines, alcohol, nicotine, and psychiatric medications such as antidepressants or antipsychotics.

Pathophysiology of NAS

The pathophysiology of NAS is rather complex and not well understood. However, altered levels of neurotransmitters are presumed to play a significant role due to abrupt cessation of trans-placental passage of opioid or other drugs/ medications exposure at birth.

Repeated exposure of opioid leads to increasing production of adenylyl cyclase with further inhibition of C-AMP production. After removal of the opioid, the inhibition of adenylyl cyclase is reversed, resulting in overproduction of C-AMP during subsequent withdrawal exposures. The resultant flux of C-AMP is suspected to cause the intense withdrawal manifestations, in addition to effects from dysregulation of other neurotransmitters.

Clinical features of NAS

This is variable and depends on: Type(s) of drug(s)/ Medication(s) taken, the amount taken, the pharmacokinetics of the drug, net transfer of drug across the placenta, placental metabolism, time between maternal drug use and infant delivery, maternal and infant metabolism and excretion, gestational age (GA) at birth and other unidentifiable factors.

Preterm infants have been described as being at lower risk of drug withdrawal with less severe and/or prolonged course of NAS with lower GA correlating with a lower risk of neonatal withdrawal and reduced adverse outcomes.

The apparent decreased severity of signs in preterm infants may relate to developmental immaturity of the CNS, differences in total drug exposure, or lower fat depots of drug. Furthermore, the clinical evaluation of the severity of abstinence may be more difficult in preterm infants, because scoring tools to describe withdrawal were largely developed in term or late preterm infants.

Table 3: Symptoms and Sign of Opioid Withdrawal

CNS	Autonomic	GIT
Neurological excitability with tremors, irritability, wakefulness, high-pitched cry, Hypertonia, Hyperreflexia Exaggerated Moro's reflex.	Sweating Nasal stuffiness Sneezing Fever Mottling Frequent yawning Temperature instability Mild elevations in respiratory rate and blood pressure Seizures	Poor feeding or excessive feeding, Uncoordinated and constant sucking, Vomiting, Diarrhoea, dehydration Poor weight gain.

Table 4: 'Withdrawal' Features of other Drugs

Cocaine & Amphetamines (CNS stimulants)	Alcohol
Irritability, Hyperactivity, Tremors,	Hyperactivity, crying, irritability, poor suck, tremors, seizures; onset of signs at birth, poor sleeping pattern, hyperphagia,

High pitched cry Excessive sucking	Sweating
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When do symptoms/signs of NAS start?

Onset of withdrawal depends on the dose taken, half-life of the drug, duration of the addiction and time of last maternal dose prior to delivery. On average, observation period for symptoms to appear is about 24-72 hours (**Table 2**)

Table 2: Maternal Misused Drugs and/or Medications and Onset of Withdrawal symptoms

Drug	Appropriate time of onset
Alcohol	<ul style="list-style-type: none"> • 3-12hrs
Benzodiazepines	<ul style="list-style-type: none"> • Few days to 3weeks
Cocaine	<ul style="list-style-type: none"> • 24-48hrs; • Usually no withdrawal signs but neurobehavioral abnormalities (decreased arousal and physiologic stress)
Heroin (short half-life)	<ul style="list-style-type: none"> • Within 24 hours
Other Opioids (buprenorphine (Subutex), codeine, Morphine, hydrocodone, hydromorphone, oxycodone, Pethidine)	<ul style="list-style-type: none"> • 24-36 hours but can be up to 5-7 days
Methadone (long half-life)	<ul style="list-style-type: none"> • Within 3 days but up to 5-7 days; • Rate of severity of withdraw does not correlate to maternal dose. Exposure is associated with longer duration of pharmacotherapy for NAS than Heroin
Methamphetamines	<ul style="list-style-type: none"> • 24-48hrs; • Usually no withdrawal signs but neurobehavioral abnormalities (decreased arousal, increased physiologic stress, and poor quality of movement)
Marijuana	<ul style="list-style-type: none"> • Usually no clinical withdrawal signs

Scoring System (See Appendix 1 for full details and key points)

Several scoring systems are available for use; however, the most widely validated and commonly used is the Finnegan Scoring System (Appendix 1). This 21-item scale, a modified version of the original created in 1975, evaluates multiple signs related to NAS and helps to guide treatment initiation and dosing. Scoring is to quantify the severity of symptoms to determine the need for pharmacologic intervention.

Literature shows that a standardised NAS scoring system is associated with a shorter length of stay and length of treatment. However, no studies to date have compared the use of different withdrawal score thresholds for initiating pharmacologic intervention on short-term outcomes.

Key points when scoring:

Due to its subjectivity the following Key Points should be borne in mind with the scoring:

- The first abstinence score should be recorded at approximately two hours after birth on infants with known in-utero drug exposure.

- Scoring should be started upon suspicion of withdrawal (see table 3) in infants with unknown maternal drug history.
 - Following the baseline score all infants should be scored at 4-hourly intervals if score remains <8
 - Scoring should reflect the baby's condition observed during the scoring interval, that is, since the last score was recorded, not just at the time of scoring and an assessment after a feed
 - In a term baby, scoring should be performed 30 minutes to one hour after a feed, before the baby falls asleep.
 - A crying infant should be soothed and quietened before assessing muscle tone, Moro reflex and respiratory rate.
 - If the infant's score at any scoring interval is > 8, scoring is increased to 2-hourly and continued for 24 hours from the last total score of 8 or higher
 - If the 2-hourly score is ≤7 for 24 hours then scoring intervals may change to 4-hourly
 - If pharmacotherapy is required the infant is scored at 2 or 4-hourly intervals, depending on whether the abstinence score is less or greater than 8 throughout the duration of therapeutic period
 - If, after cessation of pharmacotherapy the scores are persistently less than 8 for 24-48 hours then scoring may be discontinued and baby can be discharged home
- There should be formal training on the use of the MFS, organised by midwifery or neonatal training team, as stated by the authors of the MFS

Differential diagnosis

Certain conditions may mimic or confound NAS and therefore may require investigating to help rule out as a cause of the NAS-like presentation:

- Infection.
- Hyperviscosity syndrome (from polycythaemia)
- Metabolic disorders such as hypoglycaemia, hypocalcaemia, hypomagnesaemia
- Jitteriness from metabolic disorders and polycythaemia
- Hyperthyroidism
- Seizures ?cause
- Intracranial pathology – haemorrhage, ischaemia,
- Consideration should be given to NAS due to barbiturates and antidepressants such as SSRI

Investigations

The following babies may require the following investigation(s):

Table 5: List of suggested Investigations and Indications

Investigation	Indication
<p>Urine toxicology</p> <ul style="list-style-type: none"> - Send to biochemistry (use universal urine container) minimum 1 ml of urine from cotton wool pad placed in the nappy - To be collected as soon as possible after birth, as many 	<ul style="list-style-type: none"> • All cases of maternal drug misuse/ methadone programme; • Requested by Social services (SS) with documentation; • Part of clinical care after consent from the mother <p>**Results must take into account any prescribed drugs given to mother during labour</p>

drugs are rapidly metabolized and eliminated	**Collection should follow a Chain of Custody (see Appendix 3 for sample) procedure as a form of quality assurance/medico-legal requirement
Cranial Ultrasound	<ul style="list-style-type: none"> • Maternal cocaine use • Persistently abnormal CNS findings • Seizures
MRI	<ul style="list-style-type: none"> • Abnormal Cranial Ultrasound • Seizures • Persistently abnormal CNS findings
Blood/ Serum Glucose Calcium, Magnesium, Urea and electrolytes, FBC	- Excessive jitteriness or NAS-like presentation

Antenatal Management of Pregnancies/Foetus at Risk of NAS

Categories of Mothers/ Babies:

1. Mothers on prescribed medications likely to cause NAS/NAS-like features in babies
2. Mothers on Methadone Drug/ Alcohol Programme
3. Clinical concerns of possible NAS
4. Mothers with suspected illicit drug use, known to Social Services, with pre-birth care plan.

Consider the following management plan as appropriate (according to your local protocol):

1. Antenatal Counselling: for mothers in category 1&2 above, there should be a discussion between the mother, obstetrician and/or Senior Neonatal Team member on effects of such medication on the unborn and newborn baby.
2. Alerting the Neonatal Team
3. Involvement of the Midwifery Safeguarding Team/ Drug liaison midwife or team or anyone in a similar role (categories 2-4 above)
4. Multi-disciplinary antenatal plan (involving Social Services, Midwifery Safeguarding Team/ Drug liaison midwife or team /Midwifery staff, Obstetrician/ neonatal liaison, Health visitor (HV) and GP) in place for unborn baby and mother
5. Liaison with the Drug and Alcohol Services and Social services as appropriate
6. Smoking cessation counselling where appropriate

*Contact Details of local team should be made available - **See Appendix 2**

Delivery/perinatal Management

- There is no requirement for neonatal team to be present for the delivery of a maternal drug misuse/use case unless there are other indications.
- Avoid the use of Naloxone in case of respiratory depression as this may precipitate an acute withdrawal and seizure (1 case report).
- Follow local protocol as appropriate.

Postnatal Management

A. After delivery follow local protocol as indicated, including:

Information sharing, in selected cases as appropriate: informing neonatal team, social services, midwifery team with responsibility for safeguarding, Health Visitor (HV), Community Midwife (CM), Drug liaison midwife and GP (pre-discharge)

- Neonatal team to obtain the following information:
 - Drug names, route, dose, frequency and duration
 - Timing of last dose
 - Details of any drug detoxification programme/ Drug and Alcohol Services, including the gestation at which it was started
 - Other drugs/ alcohol used
 - Drugs given to mother during labour
 - Family/ social history to include number of children living with parents/ foster care/ adopted or any social services involvement
 - Establish who has parental responsibility
 - Booking and recent bloods including HIV, Hepatitis status of mother/ partner
 - Maternal history of mental illness and medication(s)
 - Record other problems during pregnancy and delivery

B. Initial Management:

- There should be a clear plan from the antenatal team, Social Services, Drug and Alcohol team, Safeguarding team or any other medical staff involved in or aware of concerns in the mother's notes.
- Documentation and any advice given to parents of babies who do not require any form of formal observation should be made in baby's notes/ or NIPE examination
- Inform CM, HV and SS of baby's progress as appropriate
- Observe as per local protocol on: NICU/SCBU/Postnatal ward/ Transitional care or as stated in the antenatal care plan
- Babies should only be separated from their mothers and admitted to NICU/SCBU if there are social, legal or medical reasons identified antenatally or for collection of urine (the urine collection needs to follow a chain of evidence pathway)
- The parents should be:
 - Involved in all care planning and delivery of care to their infant unless otherwise stated in pre-birth SS plan
 - Given every opportunity to discuss their baby's care and any concerns that they may have with the paediatrician and nursing staff
- Infants at risk of NAS or those whose mothers are suspected drug users should have the first withdrawal assessment using the Modified Finnegan Score(MFS), recorded at two hours of age (Appendix 1 for details and key points)
- Neonatal team should be made aware of any baby who starts exhibiting signs of withdrawal and admission to NICU should be considered (if scores are high and treatment is required).
- For babies whose mothers are on the Drug/ Methadone/ Alcohol Programme, known to misuse drugs, or in suspected cases of withdrawal and for those with antenatal plans to do so, some form of investigation may need to be carried out (see Table 5 above)

Admission Criteria

Criteria for admission when baby is monitored on TC/PNW:

- Baby is to be admitted to SCBU/NICU for monitoring and potential treatment if the score is ≥ 8 at any scoring interval
- Seizures
- Very unsettled, with continuous or intermittent high-pitched cry
- Poor feeding
- Other clinical concerns

Length of observation period when pharmacotherapy is not needed:

- Known Opioid-exposed infants should be observed for minimum 72 hours after birth, however the withdrawal symptoms might present as late as 14 days after birth
- Marijuana : No observation period required
- Cocaine: Babies may need to be monitored for cocaine effects for 48 hours
- Poly-drug misuse: Minimum of 72 hours

Supportive/Non-Pharmacological Management

Regardless of the need for medication for the treatment of NAS, all drug-exposed infants should receive individualised non-pharmacologic supportive management, as NAS per se is not defined solely by the need for medication therapy. Initial management should primarily be supportive for symptom scores of less than 8. If, after the period of observation the baby is asymptomatic, he/she could be discharged home, provided that any possible social concerns have been addressed and resolved.

A. General Adjunctive Therapy:

Table 6: Adjunctive Therapy

Include:	
Soothing techniques	non-nutritive sucking using 'dummy' positioning/swaddling/ gentle movement/ rocking
Maintaining temperature stability	Appropriately clothed to avoid sweating
Minimal sensory stimulation	Do not disturb when asleep; minimal noise
Minimal Environmental stimulation	Dimmed lights/ use of developmental care principles
Frequent small feeding	3 hourly feeds
May require higher feed volume and/ or higher	This may be necessary to meet the high caloric requirements to ensure proper growth and should be

caloric formula	individualised
May have "sore bottoms"	Use (for example): Paraffin 50/50 , Medihoney barrier cream (or as per local protocol)

B. Nutritional Management:

- NAS infants may have a voracious appetite/ hyperphagia and hyperactive sucking action which can lead to excessive weight gain. Others may have poor suck coordination making it difficult to establish oral feeding and supplementary tube or cup feeding may be necessary
- Observe for signs of dehydration in case of persistent vomiting or loose stools and manage as appropriate
- Infants may be prone to weight loss and failure to thrive secondary to caloric expenditure caused by their hypermetabolic state or through vomiting, possetting and loose stools.
- There is increasing evidence that using lactose free formula improves the stool consistency and perianal excoriation. This should be considered in formula fed infants.
- Breast feeding should be advocated as it may reduce the severity of withdrawal symptoms
- If the baby is not to be breast-fed then frequent small volume feeding with hyper-caloric formula to supply the additional caloric requirements may be needed
- Monitor weight at regular intervals according to local unit policy

C. Breast Feeding (BF):

BF has been shown to have several advantages including significantly reducing length of hospital stay, encouraging and improving bonding, lessening the severity of symptoms, reducing the duration of NAS and the need for withdrawal pharmacotherapy compared with formula-fed infants. The mother should be given all the necessary information to be able to make an informed choice

Table 7: Indications and Contraindications to BF

Indication	<ul style="list-style-type: none"> ➤ Should be encouraged in mothers who are stable on methadone, however, advice to avoid breastfeeding within first 2hrs post-dose ➤ In mothers with concurrent hepatitis B or C, breastfeeding is not contraindicated (not known to be transmitted through BF) and especially if baby has been immunised
Relative contraindication	<ul style="list-style-type: none"> • Mothers on high dose methadone
Contraindication	<ul style="list-style-type: none"> • HIV positive mothers • Ongoing maternal cocaine, heroin, amphetamine use • Known poly-drug misuse (or confirmed on urine toxicology in either the baby or the mother) • On IV Opioids • CNS stimulants: Eg. Dexamphetamine, Methylphenidate

D. Parent Education:

It is important for the mother and family to understand the neuro-behaviour in their infant. They need to begin building skills to help their infant cope whilst still in hospital.

Topics to discuss with mother include:

- Exaggerated rooting does not always indicate hunger
- Infants may be disturbed by normal household noises and may not sleep well
- Crying may be high-pitched
- Hypertonia may persist and mother may interpret this as sign of rejection
- Drugs that pass through into the breast milk

C. Maternal Therapy:

Mothers who are not emotionally stable or not receiving appropriate medication and/or therapy are at high risk for relapse to drug use, neglect, or abuse of the child.

The population of substance exposed infants and their caregivers is a complex and vulnerable group. Only through coordinated, comprehensive, and compassionate care can the difficulties created by in-utero substance exposure for the mother and the infant be overcome.

The following should form part of Maternal Management while baby is on the NICU:

- Agreed social services plan should be followed if in place
- Ensure adequate drug-misuse therapy is on-going
- Effective communication strategies; parents should be given opportunities to discuss on-going care, honest feedback; frequent maternal–infant assessments.
Reassurance and support are also important.
- Ensure on-going psychiatric care if required
- Encourage and supporting mother to care for the baby; it is important to prepare the mother to identify her feelings about an infant with NAS and to practice the emotional responses that will allow her to support the infant's recovery. Early experiences, such as positive caregiving during critical periods, can induce programming or reprogramming of key adaptive systems, such as stress response, that promote positive adaptation in young children that can result in healthier developmental, behavioural, and social–emotional trajectories
- Psychological care/ use of counsellors if available
- Offer rooming in pre-discharge
- Discuss follow-up plans pre-discharge

These techniques may be adequate treatment for some infants with NAS; however, pharmacological intervention is often necessary.

Pharmacological Management

Goals for initiating pharmacotherapy are to:

1. Ameliorate the clinical manifestations of withdrawal- hyperactivity and autonomic instability
2. Restore normal pattern of newborn activities, such as sleeping, feeding and consistent weight gain

Criteria and Indications for starting pharmacological treatment include:

1. Using MFS: the need for medication is indicated when:
 - The total score is 8 or higher for 3 consecutive scorings. Once the score is 8 or higher the scoring intervals automatically become 2 hourly, so significant symptoms are treated within 4-6 hours.
 - Two consecutive scores of 12 or higher require therapy to be initiated. If the score is 12 or higher the baby must be assessed by 2 people individually.
 - When the sum of 3 consecutive Finnegan scores is > 24.
2. Seizures
3. Continuous high-pitched cry (see Appendix 1)
4. Inability to feed and rest (i.e. the infant sleeps less than one hour after feeds)
5. When there is profuse diarrhoea and frequent vomiting, poor feeding and poor weight gain (when other causes are ruled out), start treatment even if scores are < 8

Pharmacotherapy:

Numerous medications have been used to treat NAS including Benzodiazepines, Chloral hydrate, Chlorpromazine, Clonidine, Morphine, Methadone and Phenobarbital. However, there are very few quality RCTs and other less robust evidence to prove the superiority of one agent above the other. Current evidence point to the increasing trend in trials and use of Morphine and Clonidine, with decreasing use of other agents (Appendix 4: Trends in Current Pharmacotherapy used in NAS). Further evidence in support of this is provided in Appendix 5: Evidence Summary Table.

- **1st line: Oral Morphine +/-**
- **2nd line/ Adjunctive Therapy: Clonidine or Phenobarbital** (*these have also been used as monotherapy in some trials and been compared to each other and to Morphine) (See Appendix 5: Evidence Summary Table)

Table 8: Medications, Dose and weaning process

	Drugs	Start, Increments, Maximum dose	Weaning Process	Dose at which to Stop
A.	1 st Line			
	Morphine			

	<p>Opiate Mu agonist Drug of choice for all opiate withdrawal 1st line for seizures 2^o to opiate withdrawal, polydrug misuse</p> <p>Monitor: 4-6hrly Respiratory rate Heart rate Blood pressure</p>	<p>Start: 50mcg/kg/dose orally</p> <p>Frequency: 3-4hrly dose regime</p> <p>Increments: 20%/dose</p> <p>*Max dose: 1000mcg/kg/day (167mcg/kg 4hrly)</p> <p>* Units using a max daily dose of <400 mcg/kg/day were more likely to require the addition of 2nd line Rx (O'Grady et al)</p>	<p>1.Reduce dose by 10-20% every 24-48hrs if all scores <8 in preceding 24hrs until reaching starting dose of 50mcg/kg/dose 3-4hrly</p> <p>2. Then decrease frequency: from 4 to 6 to 8 to 12 hourly</p>	<p>When total dose/day 125mcg/kg/day or less</p> <p>Advantages: -Very effective in opiate-related NAS</p> <p>Disadvantage: -Respiratory depression -Sedation -Frequent dosing</p>
<p>B.</p>	<p>2nd Line</p>	<p>Indications for starting:</p> <ol style="list-style-type: none"> 1. When close to or at maximum Morphine dose 2. Poly-drug use 3. To shorten duration of Morphine use/days 4. To help reduce persistently high MFS 5. Found to help reduce the dose of Morphine required 		
<p>1. Clonidine:</p>				
	<p>Centrally acting α_2-adrenegic agonist Monitor: BP and HR 4-6hrly for 48hrs after starting, then 12hrly and back to 6hrly when weaning till 24hrs after stopping</p>	<p>Start: 6mcg/kg/day orally (give 1mcg/kg then assess blood pressure before increasing the dose)</p> <p>Frequency: 4-6hly dose regime</p> <p>Increments: 25%</p> <p>Max: 12mcg/kg/day</p> <p>Clonidine may not be readily available as it is an unlicensed special drug</p>	<p>Weaning: Wean off Morphine first</p> <p>Start weaning after 48hrs off Morphine</p> <p>Decreased by 10% 24hrly</p>	<p>Stop: 1.5mcg/kg/day or less</p> <p>Advantages: -Quicker wean -In combination with Morphine, reduces MFS quicker, reduces total Morphine dose required, shortens length of stay -Shorter therapy time compared to Phenobarbital -No sedative effect -No respiratory depression</p> <p>Disadvantages: Frequent BP, HR monitoring</p>
<p>2. Phenobarbital</p>				
	<p>Barbiturate Decreases hyperactivity in CNS *May be used as 1st Line in</p>	<p>Start options:</p> <ol style="list-style-type: none"> 1. Loading dose (*may help achieve therapeutic levels quicker): 15-20mg/kg 1st Day followed by 5- 	<p>Wean off Morphine first</p> <p>Wean over 3 months</p>	<p>Wean Phenobarbital over 3 months</p> <p>Advantages: -Quicker wean</p>

	<p>Sedative-Hypnotic withdrawal</p> <p>Monitor: Periodic Phenobarbital levels Keep levels 20-30mg/l</p>	<p>10mg/kg/day orally</p> <p>2. No loading dose regime: 5-10mg/kg/day orally</p> <p>Frequency: 12hrly dose regime</p> <p>Max: 10-12mg/kg/day orally</p>	<p>-In combination with Morphine, reduces FS quicker, reduces total Morphine dose required, shortens length of stay</p> <p>Disadvantage: -Over sedation -Needs levels monitoring -Overall longer therapy time compared to Clonidine -Need for outpatient follow up and weaning -? Potential adverse effect of Phenobarbital on developing brain</p>
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Care coordinator for the baby on the NICU

- There will be close liaison between the Neonatal Team, the Midwifery Safeguarding Team, Social Services/ Social Worker, any identified keyworker, Drug liaison midwife, the Health Visitor and the GP.
- On the NICU, this will be coordinated and facilitated by a named team member, eg. Neonatal Community Nursing Team with regular updates of progress.

Discharge on home medication

Some babies (e.g. babies discharged to foster care, babies born to mothers on prescribed opioids for pain management) may be discharged home on medication, once symptom control has been achieved:

- Morphine (weaning can follow the above regime)
- Phenobarbital can be weaned within 3 months

Discharge Planning

- All routine discharge procedures must be followed.
- NAS babies should have been off medications for at least 24-48hrs with NAS Scores of less than 8 before discharge.
- Exception to above is the use of Phenobarbital. Administration competency should be achieved by parents/foster carer before discharge.

In addition:

- The Neonatal Community Nursing Team will facilitate and coordinate the discharge of the babies who required treatment, in liaison with the appropriate professionals including the GP, Health Visitor, Social Worker, Midwifery Safeguarding Team, the social worker and Drug/ Alcohol Rehabilitation Team
- A discharge planning meeting should be held, where considered necessary, with parents/ family/ Foster carer (as applicable), Health Visitor, Social worker with

typed copy of the minutes to be included in the clinical notes. Local services such as Drug/Alcohol Rehab Team should also be informed. This is to allow the key workers adequate time to organise and co-ordinate post discharge substance use review and care i.e. medication, methadone / other prescribed medication (if applicable), appointment with the doctor / key worker etc.

- Complete a 'SEND' discharge summary with details of the HV, SW for GP with copies to social worker (as applicable), health visitor and the family. Care must be taken not to include any sensitive information.
- For Babies going into Foster Care, a special discharge form or letter should be devised to be given to Foster carers with detailed ongoing care or follow up plan

Follow up

- For infants discharged on Phenobarbital, there should be a weaning protocol aimed at stopping the medication within the first 3 months of age
- Arrange Paediatric/ Neonatal Consultant follow up for all the symptomatic babies who required treatment
- For babies who are discharged to Foster Care, referral to 'Looked After Children's Medical team (part of the Community Paediatric Team) for subsequent follow up should be arranged.
- It is recommended (American Association of Paediatrics guideline) for babies diagnosed with NAS, who required pharmacological treatment, to have neuro-developmental assessment at 2yrs

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Appendix 1: Finnegan Scoring System

*Separate attachment

Appendix 2: Important Contact Details (Sample)

Neonatal Intensive Care Unit High Dependency/ Special Care Baby Unit	Ext: Ext:
Neonatal Nursing Team Responsible for Drug Misuse and Alcohol	Bleep: Ext:
Named Responsible Neonatal Consultant	Neonatal Secretaries: Ext:
Neonatal Consultant on-call	Bleep Ext:
Neonatal Sister-in-charge	Bleep: Ext:
Midwifery Team with responsibility for Drug and Alcohol Misuse	Bleep: Ext:
Local Social Services Team	
Local Drug and Alcohol Services/Treatment Team	Tel:
Other staff contact as required	Tel: Bleep:

Appendix 3: Chain of Custody Form: Urine Toxicology (Sample)

Hospital Logo

Patient label/ Details

CHAIN OF CUSTODY FORM
 Department of Pathology

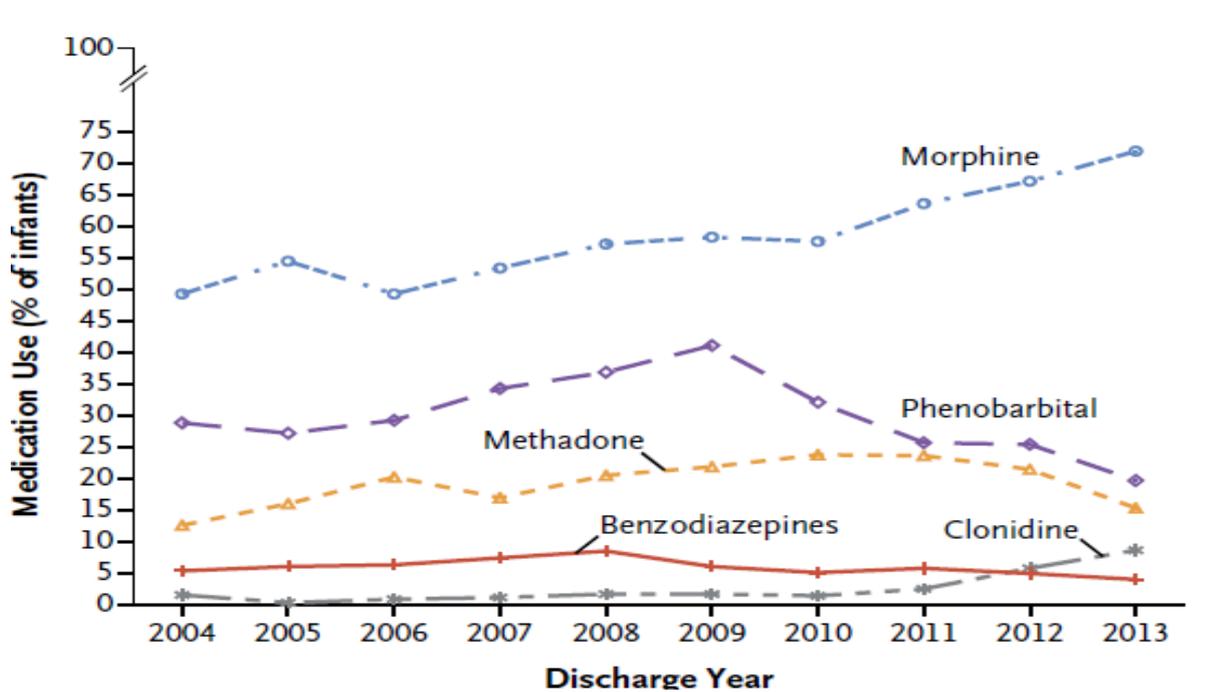
Sample Accession Number:

Date	Time	Name of person handling sample	Action taken	Signature
		Nurse:	Sample taken	
		Porter:	Sample sent to lab	
		Lab reception:	Sample received Accession number allocated	
		Lab technician:	Sample analysed	
		Etc		

**The form should accompany the sample until after analysis of the sample and results put in the patients lab results system

Appendix 4: Trends in current pharmacotherapy used in NAS management
Increasing use in Morphine and Clonidine, with decreasing use in all other agents

(Tolia V, Patrick S, Bennett M, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med.* 2015;372:2118-2126)



Appendix 5: Evidence Summary: Trials/ Case Series using/comparing Morphine, Clonidine & Phenobarbital

	Study/Trial/Case series (All term or near term infants)	Medication & Dose	Weaning Protocol	Minimum dose at which it was stopped
1	<p>Surran et al 2013, J Perinatology</p> <p>Non-blinded RCT Opiate exposed infants 34 infants in each arm Grp 1: M+Clonidine OR Grp 2: Phenobarbital MFS >8 x2 3hr apart Opiate exposure + poly drug use</p> <p>BP 6hly for 48hr then 12hly; back to 6hly when on Clon alone till 24hrs after coming off</p>	<p>Morphine: Start 320mcg/kg/day = 40mcg/kg 3hly Max 800mcg/kg/day = 100mcg/kg 3hly +</p> <p>Phenobarbital: Start 6mg/kg/day Max 12mg/kg/day 8hrly doses</p> <p>Versus</p> <p>Clonidine: Start 6mcg/kg/day 6hly dosing</p> <p>Max 12mcg/kg/day</p>	<p>Weaned Morphine first Reduce dose by 10% every 24hrs if all scores <8 in preceding 24hrs</p> <p>Phenobarbital Weaning schedule after discharge</p> <p>Clonidine Started weaning 24hrs after stopping Morphine</p> <p>½ the dose every 24hrs and stop at 1.5mcg/kg/day</p>	<p>Morphine 120mcg/kg/day</p> <p>Phenobarbital Stopped at home</p> <p>Clonidine 1.5mcg/kg/day</p> <p>Results: Both study grps showed Shorter duration of stay compared to pre-trial Morphine monotherapy. Phenobarbital compared with Clonidine had shorter Morphine Rx days with no difference in average Morphine total dose (therefore comparable efficacy in NAS Rx). Post-discharge, Phenobarbital was continued for an average of 3.8 months. 2pts in Clonidine group failed weaning 7 successfully Rx on Phenobarbital 3 pts in Phenobarbital grp showed signs of over sedation No CVS adverse effects in Clonidine group</p>
2	<p>Bada et al, 2015; Pediatric</p> <p>Pilot Prosp double-blind RCT 15 and 16 pts in each arm respectively</p> <p>Known prenatal opiate exposure</p>	<p>Morphine: Start: 400mcg/kg/day in 3hly doses= 50mcg/kg/dose 25% increase/day Max 1000mcg/kg/day = 125mcg/kg 3hly</p>	<p>Morphine: Weaned Morphine first, 10% dose reduction 48hly</p>	<p>Morphine: When dose <100mcg/kg/day</p> <p>Clonidine: When dose <1mcg/kg/day</p>

	<p>Morphine monotherapy OR Clonidine monotherapy</p> <p>Urine toxicology only opiate and few Benzodiazepine</p> <p>MFS >8 x3 3hrs apart or >12 x2</p> <p>Addition of 2nd drug when max daily doses reached BP monitoring</p>	<p>Clonidine: Start: 5mcg/kg/day 3hly = 0.625mcg/kg</p> <p>25% increment/ day Max 12mcg/kg/day 1.5mcg/kg 3hly</p>	<p>Clonidine: 10% dose reduction 48hly</p>	<p>Results: Rx duration was significantly longer for Morphine than Clon Neuro-behavioural scores (NNNS) improved significantly with Clonidine but not with Morphine. On subsequent assessment, those receiving Clonidine had lower height of arousal and excitability. No infant in the study required a 2nd medication</p>
3	<p>Agthe et al, 2009 Pediatrics</p> <p>Double blind RCT Exposure to Methadone or Heroin 40 pts in each arm</p> <p>Morphine+Clonidine OR Morphine+Placebo</p> <p>1^o outcome = Duration of M therapy Used MFS of ≥9 on 2 occasions</p> <p>BP, HR monitoring</p>	<p>Morphine: Start: 200mcg 4hrly</p> <p>Increment: 100mcg/dose</p> <p>Max dose: 900mcg 3hrly</p> <p>Clonidine: Start: 1mcg/kg/4hly = 6mcg/kg/day</p> <p>Increment till Max 12mcg/kg/day</p>	<p>Weaned Morphine first Start after 48hrs of control; decreased by @ 14% 24hrly</p>	<p>Not clear</p> <p>Results: Shorter duration of Rx and lower total dose for Morphine+Clonidine group. 5 Rx failure in the Morphine+Placebo group, none in M+C grp. HR and BP lower in Clonidine group but within normal range</p>
4	<p>Esmaili et al, 2010, Acta Paed.</p> <p>Retrospective Review Exposure: Mothers on Methadone Program Comparing combination Rx of:</p> <p>Clonidine+/-Chloral Hydrate (29pts; PICU setting) Vs Morphine+/-Phenobarbital (64 pts)</p> <p>2nd agent, i.e., chloral and Phenobarbital is only added when max dose of 1st agent Clonidine or Morphine is reached</p> <p>Used MFS >10 x1 BP monitoring</p>	<p>Clonidine: IV infusion Start 12mcg/kg/day Max 72mcg/kg/day +/- Chloral Hydrate: 30-50mg/kg/dose max TDS</p> <p>Morphine: Start 300mcg/kg/day Max 800mcg/kg/day +/- Phenobarbital BD dosage 20mg/kg/day 1st day 5mg/kg/d from 2nd day Max 10mg/k/day</p>	<p>Stepwise increase, rate not stated</p>	<p>Stop: Not stated</p> <p>Results: Rx duration significantly shorter in clonidine/chloral hydrate group & group also exhibited markedly reduced withdrawal symptoms. BP was comparable in the 2 groups</p>
5	<p>Jackson et al. ADCFN 2004</p> <p>Double blind RCT on Rx for NAS</p> <p>Exposure: Opiates and other drugs</p> <p>Morphine (41 pts) Vs</p>	<p>Start: Morphine 50mcg/kg QDS Vs Phenobarbital 2mg/kg QDS (no loading dose**)</p> <p>Increments:</p>	<p>Wean: 20% decrease in dose every 48hrs (not the decrease in frequency)</p>	<p>Stop: Not clear</p> <p>Results: Morphine grp required fewer days active Rx. Maternal methadone dose independently influenced the duration of Rx</p>

	<p>Phenobarbital (34 pts)</p> <p>Used Lipsitz tool for scoring</p>	<p>20% increase in dose</p> <p>Adjunct Medication: Chloral Hydrate 15mg/kg</p> <p>** Kaltenbach & Finnegan compared 36 drug exposed infants treated with Phenobarbital regimens that did or did not use a loading dose. No significant difference was identified between regimens</p>		<p>Infants receiving Phenobarbital grp tended to require an additional drug more often</p> <p>Other factors also appeared to correlate with the requirement for second line Rx, including: maternal methadone dose, in utero exposure to classes of drugs other than opiates or benzodiazepines, and exposure to benzodiazepines</p>
6	<p>Coyle et al. 2002, J Ped,</p> <p>Partially RCT 20 cases, 10 each arm</p> <p>FS >7</p> <p>Combination of Morphine+Phenobarbital Vs Morphine alone</p> <p>Monitored: ECG, HR, electrolytes and Clonidine levels</p>	<p>Start: Morphine 50mcg/kg/dose 3-4hrly (0.4mg/ml) Increments:: 0.1ml = 125mcg</p> <p>Phenobarbital Loading 10mg/kg 12hrly x3 Maintenance 2.5mg/kg BD to achieve blood levels of 20-30mg/dl (previously been shown to control NAS symptoms in 94% of patients)</p>	<p>Wean: Morphine by 0.1ml if FS<5 8hrly x3</p> <p>Phenobarbital: weaned by GP over 2-9 mon</p>	<p>Stop: Not clear</p> <p>Results: The duration of stay was reduced by 48% for the Morphine and Phenobarbital group; these infants spent less time with severe withdrawal, and required a lower max daily Morphine dose when compared with the Morphine-only group. The mean duration of outpatient Phenobarbital use was 3.5 months.</p>
7	<p>Kandall D et al Am J Dis Child.</p> <p>1983 RCT</p> <p>Morphine (49 pts) Vs Phenobarbital (62 pts)</p> <p>42 randomised pts did not require any Rx</p> <p>Exposure: maternal opiate and ½ in each grp abused other drugs</p> <p>Used Lipsitz scoring system</p>	<p>Start: Morphine: 80mcg/kg 3hrly</p> <p>Increment: 20mcg/dose</p> <p>Max not given</p> <p>Phenobarbital: 5mg/kg/day in 8hrly doses</p> <p>Increment: 1mg/kg/day until symptom control Max not given</p>	<p>Weaning: Starts 5 days after symptom control By 20mcg/kg/dose</p>	<p>Stop: Not stated</p> <p>Results: Both Morphine and Phenobarbital controlled symptoms equally well; 7/62 Phenobarbital treated newborns had abstinence-associated seizures within the first month of life, 42 neonates initially requiring no Rx were born to mothers taking less methadone just before delivery, however 5/42 had seizures within the first 14 days of life</p>
8	<p>Hoder et al. N Engl J Med.1981 and Hoder et al. Psychiatry Res. 1984</p> <p>2 Separate Case series Both used Clonidine</p>	<p>Both case series started Clonidine at: 0.5-1mcg/kg 4-6hrly Titrated up towards maintenance dose of 3-5mcg/kg/day in 4-6hrly doses</p>	<p>25% decrease in total dose every 48hrs</p>	<p>Stopping dose not started: Minimum dose used was 0.5mcg/kg 6hrly</p> <p>Results: Achieved Rx in 6/7 in each case</p>

	<p>monotherapy 7 infants in each case series were exposed to maternal Methadone Used Finnegan Scoring system</p>			<p>series at highest maintenance dose The 2 failed Rx had been exposed to Haloperidol, Desipramine and Theophylline. Mean length of Rx 13 in one case series and 12.2 days in the other (ranges 6-27 and 6-17 days) Clonidine levels did not correlate with symptom control No adverse effects were noted</p>
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Appendix 6: Audit of Practice

A list of all Babies admitted to the Neonatal Unit/ Transitional Care for NAS management and for Urine Toxicology sample taken, should be kept by the Neonatal Team

Auditing Tool/ Proforma (Sample)

Hospital Number	
Date of birth	
Social Services involvement	Yes [] No []
Antenatal plan in place	Yes [] No []
Maternal details	
<p>Maternal</p> <div data-bbox="183 1160 662 1368" style="border: 1px solid black; border-radius: 15px; padding: 10px; text-align: center; color: red; font-weight: bold; margin: 10px auto; width: 80%;">Patient label</div>	<p>Age: Occupation: Ethnicity: Parity: Marital status: Mental health issues: Yes [] No [] Received antenatal care: Yes [] No [] Alcohol Use: Smoking: Yes [] No [] Number/day: Serology: HIV (Y/N) Hep B (Y/N) Hep C (Y/N)</p>
Reason for admission	
1. Known maternal drug misuse If on Methadone programme- Daily dose	Name of Drug(s):
2. Suspected maternal drug misuse/ Suspected NAS in infant If on Methadone programme- Daily dose	Name of Drug(s)
3. Maternal medication	
Baby	

Patient label

	Gestational Age: Gender: Weight: Centile: Head Circumference: Centile:
Date & Day of admission	
Date & Day of discharge	
Total number of Days on the Unit	
Date, time & Day Urine Sample obtained	
Was mother given an opioid perinatally during labour?	Yes [] No [] If Yes, name:
Urine Toxicology results with Dates	Date of Formal report: Report:
Date & Day of life Starting Morphine	
Maximum Dose of Morphine required	
Maximum score(s)	
Date and Day of life of above	
Date & Day of stopping Morphine	
Total number of days on Morphine	
Was 2 nd agent required	Yes [] No []
Name of 2 nd agent used	
Maximum dose of 2 nd agent	
Date & Day of starting 2 nd agent	
Date & Day of stopping 2 nd agent	
Treatment failure (change in 2 nd agent; symptom rebound after stopping all medication)	Yes [] No [] Change from:to
Any Adverse effect from Medication	Yes [] No [] If yes, please list:
Discharge Planning meeting held	Yes [] No []
Feeding type	Breast feeding [] Bottle [] Expressed Breast milk [] High energy formula required? Yes [] No []
Discharge	Date: Day of Life: Discharged on medication: Yes [] No [] Name of medication:
Discharged route:	Home to Parents [] Family member [] Foster care []
Comorbidity/ties during stay: List	1. 2. 3.
Follow up arranged	Yes [] No []
If infant went home on medication, age at which it was stopped	Date: Age:
2yr Neurodevelopmental outcome	

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Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

Details of person completing the form:	
Title:	Organisation:
First name:	Email contact address:
Surname:	Telephone contact number:
Title of document to be excepted from:	
Rationale why Trust is unable to adhere to the document:	
Signature of speciality Clinical Lead:	Signature of Trust Nursing / Medical Director:
Date:	Date:
Hard Copy Received by ODN (date and sign):	Date acknowledgement receipt sent out:

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