Joint Trust Guideline for the Management of Neonatal Abstinence Syndrome

A clinical guideline recommended

For use in:	Neonatal Intensive Care Unit, Post natal wards
By:	Paediatric Medical staff, Neonatal Nurses, Midwives
For:	Infants born to mothers using drugs of dependence
Key words:	Abstinence, opiate, withdrawal, Neonatal Abstinence Syndrome (NAS)
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

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Version and Document Control:

Version Number	Date of Update	Change Description	Author
3.2	21/07/2021	Minor changes only.	Dr M P Dyke

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Quick reference guideline

For use: in Neonatal Unit and Postnatal wards

For use by: Paediatric, Neonatal and Midwifery staff

For: infants withdrawing from drugs of dependence

NB: babies of mothers taking opiates or CNS depressants should be observed for 3 days minimum

Symptom scoring chart

Date												
Time												
Tremor												
Irritability												
Muscle Tone												
Cry												
Vomiting												
Diarrhoea												
Sneezing												
Fever												
Sweating												
Tachypnoea												
Total												

Perform symptom score approximately 4 hourly (or with feeds) basing score on observations over the whole 4-hour period– see below for severity ratings

Symptom	0	1	2	3
Tremor	Normal	Minimal increase when hungry or disturbed	Marked increase when disturbed – subside when fed or held snugly	Marked increase even when undisturbed
Irritability (excess crying)	None	Slight increase	Moderate/severe when hungry or disturbed	Marked even when undisturbed
Muscle tone	Normal tone	Mild to moderate increase	Rigid	
Cry	Normal	High pitched		
Vomiting	No	Yes		
Diarrhoea	No	Yes		
Sneezing	No	Yes		
Fever	No	Yes		
Sweating	No	Yes		
Respiratory rate	<55	55-75	>75	

Treatment Guidance

- Any seizure attributed to drug withdrawal should be treated.
- Consider treatment for infant with symptom score ≥5 on 2 or more occasions
- Where possible, use a drug from the same group as that to which there has been in-utero exposure

Drug	Initial dose	Dose interval (hours)	Dose increment (if required)
Morphine	50 microgrammes/kg **[max. first dose = 125 microgrammes]**	4	50 microgrammes/dose
Methadone	50 microgrammes/kg	6	50 microgrammes/dose
Phenobarbital	20 mg/kg in 2 doses [followed by maintenance 5 mg/kg/day]	24	
Chlorpromazine	500 microgrammes /kg	6	
Buprenoprhine S/L	6 microgrammes /kg	8	4 microgrammes/kg [max dose: 20 mcg/kg]

Broad Recommendations

There is more published data on NAS related to opiate/opioid usage than any other drugs. Even here, the quality of research is limited and therefore optimal evidence-based management strategies are limited in scope. For other drugs, whether prescribed or illicit, the risks, presentations and optimal management strategies are less well supported by evidence. Multiple drug use is common and this complicates significantly the assessment of effects of, and management strategies for, both individual drugs and the plethora of potential drug combinations.

Patients at risk of withdrawal effects: are infants of mothers believed or known to have taken drugs in the 3rd trimester from the following list:-

Opioids	CNS depressants
Morphine Heroin Methadone Codeine Pentazocine Buprenorphine Fentanyl	Alcohol Barbiturates Benzodiazepines Hypnotics

Those patients registered with the local Drug & Alcohol Rehabilitation Services may be known to the Midwifery and/or Neonatal Outreach team from whom details should be sought.

1. Clinical features

May vary with :-

- type of drug (record accurately all maternal drugs)
- dose ingested – although evidence suggests a relatively poor correlation between methadone dose and incidence or severity of NAS
- chronicity of use (record last known doses)
- timing of last dose
- gestational age (Term infants tend to have longer duration of symptoms)
- timing of onset of withdrawal effects is variable:
    - morphine and heroin usually produce symptoms within 24 hours.
    - withdrawal from methadone, barbiturates and benzodiazepines may take 3-4 days or, occasionally, longer.
    - an audit of practice in NNUH demonstrated that all infants who required treatment were identified by 3 days of age and this should be regarded as the minimum required period of observation in hospital for infants exposed to opiates and CNS depressants.
- drugs other than opiates and those which cause CNS depression effects in mothers may also be associated with problems in the newborn period although these are not usually a reflection of true “neonatal withdrawal/abstinence”:
    - SSRIs raise two main concerns:
        - Neonatal Adaptation syndrome: prevalence rate 10-30%, manifestations include CNS [agitation, sleeplessness, tremor, poor feeding], respiratory distress and gastro-intestinal disturbance. Symptoms are usually mild, present within hours and settle within 2-3 days. Parents should be given advice on potential symptoms and non-pharmacological management of mild symptoms

- Persistent Pulmonary Hypertension of Newborn: infants should be observed for a minimum of 24 hours and particular attention paid to the routine pulse oximetry screening.

- anti-psychotic medication, particularly when used in the 3rd trimester ,may produce a syndrome of extra-pyramidal effects in newborns, including agitation, hypertonia, hypotonia, tremor, somnolence, feeding problems and respiratory distress
- illicit stimulant drugs [eg amphetamines and cocaine] most commonly produce short-lived, self-resolving episodes of mild CNS disturbance [poor sleep, fist sucking, jitteriness, high pitched cry +/- tachypnoea] lasting up to 3 days. Treatment is not required
- cannabis effects are less common and milder but may persist for several weeks

2. Typical symptoms of opiate withdrawal

CNS	GIT	Autonomic	Other
Wakefulness Irritability Tremors High pitched cry Increased tone Brisk tendon reflexes Seizures Myoclonic jerks	Poor feeding Excessive feeding Vomiting Diarrhoea Poor weight gain	Yawning Sneezing Fever Hiccoughs Sweating	Tachypnoea Apnoea Skin excoriation

Remember – it is very important to consider other diagnoses to explain the presenting symptoms:

- infection
- hypoxic-ischaemic encephalopathy
- electrolyte imbalance (Na, Ca, Mg)
- hypoglycaemia
- peri-ventricular haemorrhage.

The scoring sheet should be used to document symptoms every 4 hours or when the baby wakes for feeds. The score attributed for each symptom should be based on an assessment of the overall picture for the period since the previous score was recorded, NOT on a single observation.

3. Treatment

- **Non-pharmacologic**
  - measures should be taken to minimise disturbance and optimise comfort :-
    - swaddling
    - nurse in prone position

- ♦ decrease sensory stimulation
  - minimise handling
  - reduce noise exposure
  - reduce light exposure
- ♦ give frequent small feeds: these babies may need a volume intake slightly higher than usual, sometimes up to 200 mLs/kg/day. However, excessive feeding may be a sign of distress, reflecting inadequate symptom control and can, of itself, lead to symptoms [eg abdominal pain or vomiting] so should be avoided
- ♦ where necessary, adjust fluids and electrolytes to account for abnormal losses

- **Pharmacologic**
  - there is a paucity of long-term outcome data on the benefits or otherwise of drug treatment.
    - ♦ established benefits - short term amelioration of symptoms
    - ♦ potential drawbacks - longer exposure to drug of dependence
      - usually a longer hospital stay
  - no randomised controlled studies have shown marked consistent benefit for any particular drug although there is some evidence that opiates reduce seizures, the time to regain birth weight and duration of supportive care.
  - symptoms probably respond best to a drug from the same group as that to which there has been in-utero exposure.
  - **Opiates:** for opiate exposure unit policy is to give Morphine initially:
    - drug treatment should be considered if the symptom score is ≥ 5 on 2 or more occasions at least 4 hours apart, despite optimal use of non-pharmacologic treatment
    - treatment should be started at standard doses and subsequent doses titrated against the response
      - if significant symptoms persist despite 2-3 consecutive doses the next dose should be adjusted upwards (see table)
      - if the infant is unduly sedated with standard doses, the treatment should be withheld and, if symptoms recur, re-started at a lower dose.
    - excessive weight loss or failure to thrive should be considered as an important sign of inadequate treatment, particularly if the baby is on a high calorie intake (eg feed volume of >200 mLs/kg/day)
    - alternative/complementary strategies:
      - there is some published evidence in support of the use of sub-lingual buprenorphine in place of oral morphine but currently no standard formulation exists
      - clonidine may be used either as single agent or adjunctive treatment in opiate withdrawal. It may shorten hospitalisation and/or duration of

- morphine treatment but increase the risk of rebound symptoms on discontinuation

- **Benzodiazepines:** when benzodiazepines have been used in pregnancy, babies may be treated with Diazepam after discussion with a consultant. There is no good published evidence regarding optimal dosage; it is usual to start with a conservative dose and titrate upwards if required (see table)
- **Multiple drug exposure:** where an infant has been exposed to multiple drugs, start with morphine; if morphine alone proves insufficient to control symptoms, phenobarbital is the preferred second-line treatment.
- where phenobarbital is used and high doses are required, blood levels should be monitored once steady state concentration is achieved in the plasma.
- controlled drug prescriptions should be written in words as well as figures.

Drugs available to treat symptoms are:

Drug	Initial dose	Dose interval (hours)	Dose increment (if required)
Morphine	50 microgrammes /kg **[max. for 1st dose = 125 microgrammes]**	4	50 microgrammes /dose
Phenobarbital	20 mg/kg in 2 divided doses [maintenance: 5mg/kg/day]	24	
Methadone	50 microgrammes /kg	6 - 12	50 microgrammes /dose
Chlorpromazine	500 microgrammes /kg	6	
Diazepam	250 microgrammes /kg	12	100 microgrammes /kg [to max of 500 mcg/kg]

Weaning

- once symptoms have been controlled on a stable dose for 48-72 hours, begin to wean treatment.
- wean by decreasing the dose **not** by increasing the dose interval.
- decrease dose by 10-15% **of the maximum dose** that the infant has received, every 48-72 hours. If symptoms recur, this interval may be prolonged – a decision to be taken only by Consultant, senior ANNP or Registrar.

4. Breast-feeding: there are two main points of discussion:

- **Drug transfer:** all drugs of abuse transfer to breast milk but:
  - methadone transfer is now thought to be relatively modest and therefore safe.
  - for mothers on Subutex (buprenorphine) for opioid dependence, it is considered safe to breast feed but the baby will need to be monitored for signs of withdrawal and feeding problems.
  -

- for many other drugs, data on transfer into breast milk is limited. Some antidepressant medications are transferred to breast milk in significant amounts; others are considered relatively safe. Detailed advice is available in the BNF

- **Transmissible viruses**

See related protocols on:

- **HIV** (Trust Guideline for the **Management of HIV in Pregnancy (id=1185**) CA 2020/AO21and Trust Guideline for the **Management of Infants born to HIV positive mothers (id=1184)** CA2018)
- **Hepatitis B** (Guideline For Infants at risk of Hepatitis B infection (Id=1183) CA2017**)**
- **Hepatitis C** (Trust Guideline for Screening Infants and Children at risk of Hepatitis C infection id=1213, CA 2058)

It is very important to document maternal viral status and offer appropriate vaccination advice.

5. Discharge from hospital

There is good published evidence to suggest that weaning of medication can be safely achieved at home in selected cases. Potential benefits include shorter hospital stay and increased breast feeding rates; however, overall duration of treatment with medication may be longer.

Discharge of an infant receiving medication for NAS:

- is at the discretion of the consultant in charge of each case.
- should be considered if: -
  - the dose of medication required to control symptoms is stable or reducing
  - parents (or other carers as appropriate) have demonstrated a capacity to meet all the infants needs
  - in cases with which they are involved, support for early discharge is obtained from Children's services
- follow-up should be arranged as directed by Consultant

Rationale for the recommendations

Infants born to mothers who have taken drugs of dependence during pregnancy have a high incidence of symptoms of acute drug withdrawal, with considerable morbidity. The practice of treating symptomatic infants with opiate and other medications is well established and widespread. However, there is a paucity of well-conducted studies on which to base practice and, as a result considerable variation occurs in management. This guideline was originally drafted in 2001 based on a review of the available literature (medline – search on "Neonatal abstinence syndrome") and drew particularly on a consensus statement from the American Academy of Pediatrics Committee on Drugs, published in 1998. The 2003 update drew on new publications including a Cochrane Database Review and a review article by Johnson et al. It is further informed by a local audit of practice completed July 2003.The 2009, 2012, 2015, 2019 and 2021 updates offer some further clarifications and additions based on articles published since then.

Clinical audit standards

- All infants at risk of NAS should be observed in hospital (with 4-hourly symptom score) for a minimum of 3 days
- For all treated infants there should be correctly completed daily symptom score sheets for the duration of treatment
- There should be accurate documentation of maternal drug use including dosage
- Maternal viral serology status should be documented
- Drug treatment for infants should correspond to maternal drug and should comply with the Trust's Medicines Prescribing Policy and Procedures (http://intranet/depart/pharmacy/docs/MedicinesPolicy.doc)

Summary of development and consultation process undertaken before registration and dissemination

The original guideline was drafted by Dr M Dyke on behalf of a guideline development group of Paediatricians, Neonatal nurses and midwives, who agreed the final content. During its development it was circulated for comment to all Consultant Paediatricians, the NICU manager, Advanced Neonatal Nurse Practitioners and the Clinical Midwifery Manager. Potential amendments were discussed at an audit presentation to the Paediatric Dept (Jul 03) and the amended version circulated as before. The 2009 update was discussed in a guideline meeting in NICU and amendments made. Subsequent revisions have been circulated and accepted by those groups mentioned above.

This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list / dissemination method
Trust Intranet

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Appendix 1

Information Leaflet for Parents

Advice on the care of an infant whose mother has taken anti-depressant medication in pregnancy

1. What is an antidepressant?

An antidepressant is a medication prescribed by a doctor to help with mood problems, depression or sometimes other problems such as anxiety.

2. If I'm taking an antidepressant, is it safe for my baby?

There are many different types of drugs in the "family" of medications called antidepressants. Some are safe to take during pregnancy and breast feeding; others may carry a risk of causing problems. During your pregnancy, the doctor responsible for prescribing the medication will have given careful thought to the potential risks as well as benefits of the drug. Now that your baby is born, we need to consider two issues – withdrawal effects and breast feeding.

3. Will my baby have "withdrawal effects"?

During your pregnancy, some of the drug circulating in your bloodstream may have crossed through the placenta [afterbirth] to the baby. As this may have been going on for some weeks or months, the baby's system may have become used to the presence of the drug. Now that s/he is born and no longer receiving the drug, it is possible that his/her system will show signs of withdrawal of the drug such as:

- difficulty settling to sleep (remember that this is quite common in babies so, on its own, it is not likely to be a specific sign of a problem)
- irritability & high pitched cry
- poor feeding or excessive feeding
- vomiting or diarrhoea
- lots of yawning, sneezing, hiccoughs or sweating

Most babies born to mums who have taken antidepressants do not show these symptoms. If they do occur, they tend to start in the first few days of life, be mild and last for only a few days before settling on their own.

4. What can I do to help?

If your baby shows signs of being unsettled, irritable or cries excessively, reducing the amount of stimulation may help to calm him/her:

- Reduce the amount of light and noise to which s/he is exposed.
- Wrap him/her in a sheet or blanket to feel cosy [make sure not to wrap too tightly or use too much bedding so that s/he gets too hot]
- S/he may need frequent smaller feeds

If your baby is feeding poorly, or needs very frequent feeds or has vomiting or diarrhoea, you should consult your midwife for further assessment and advice

5. Is it safe to breastfeed?

Some drugs are quite safe to continue during breastfeeding; others may cause problems and should be avoided. If you are intending to breastfeed your baby, the paediatrician will speak to you to give you specific advice relevant to your individual situation.

If the particular drug you are receiving is not compatible with breastfeeding, it is generally safer for you to continue to take your medication and feed the baby using formula; you should not discontinue your treatment suddenly or without advice from your own doctor.

Contact Information: if you have any queries regarding this issue, you should speak to your midwife who will be happy to answer your questions