

Management of neonatal abstinence syndrome: a national survey and review of practice

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ABSTRACT

Aim: To ascertain the present management of neonatal abstinence syndrome (NAS) in neonatal units in the United Kingdom (UK) and Ireland.

Methods: Postal questionnaire to 235 neonatal units, with telephone follow-up of non-respondents.

Results: The response rate was 90%, and 96% of respondents had a formal NAS guideline. The median number of infants treated annually for NAS was 6 (range 1–100). The method of Finnegan was the most widely used scoring system (52%). Morphine sulphate was the most commonly used first line agent for both opiate (92%) and polysubstance (69%) withdrawal. Dosing regimens varied widely. Units using a maximum daily morphine dose of <400 µg/kg/day were more likely to require the addition of a second agent (76% vs 58%, $p = 0.027$). Phenobarbitone was the drug of choice to treat seizures secondary to both opiate and polydrug withdrawal in 73% and 81% of units, respectively. 29% of units allowed infants to be discharged home on medication. 58% of these allowed administration of opiates in the community and in almost half of cases this was managed by a parent. Mothers on methadone whose serology was positive for hepatitis B and/or C were four times more likely to be discouraged from breastfeeding.

Conclusions: The majority of units currently use an opiate as the drug of first choice as recommended. Doses utilised and second agents added vary significantly between units. Many of our findings reflect the lack of high-quality randomised studies regarding management of NAS.

Neonatal abstinence syndrome (NAS) is a constellation of symptoms and signs typically observed in infants delivered to women dependant on addictive substances during pregnancy, although withdrawal phenomena are also well recognised in relation to prescribed antidepressants.¹ Manifestations of the syndrome include irritability, high-pitched cry, tremors, hypertonicity, poor feeding, vomiting and diarrhoea. Seizures are described in 2–11% of symptomatic infants in some published series.^{2–4} Drug-exposed newborns have increased neonatal mortality from sudden infant death syndrome in the short term,⁵ particularly in the low birthweight infant.⁶ Long-term morbidity occurs in this population with regard to adverse neurodevelopmental outcome,^{7–9} strabismus¹⁰ and teratogenic effects, most notably those of cocaine (genitourinary),¹¹ amphetamines (cardiac, gastroschisis)^{12 13} and alcohol (facial and ocular).

NAS is most commonly seen in clinical practice in infants of mothers on methadone maintenance therapy for heroin addiction.¹⁴ Methadone causes a

What is already known on this topic

- ▶ Opiates are the treatment of choice for neonatal opiate withdrawal.
- ▶ Non-evidence based treatments for the condition have previously been widely used in the UK.

What this study adds

- ▶ Attitudes to breastfeeding by women on methadone and by those who have positive hepatitis serology are identified.
- ▶ Discharge of infants on medication is common and its safety requires further investigation.

more severe and prolonged withdrawal than heroin, and seizures are more likely in affected neonates (10% vs 1.5%).¹⁵ High prevalence areas such as that served by the Glasgow Royal Maternity Hospital have seen a 10-fold increase in neonatal abstinence over the past decade which has become increasingly difficult to treat.¹⁶ Polysubstance use is widespread in this population. Benzodiazepine use and cocaine abuse occur in 50%¹⁷ and 37%¹⁸ of pregnant women on methadone, respectively, with the latter in particular increasing the frequency and severity of withdrawal.¹⁹

A variety of pharmacological agents and regimens are used to treat NAS, reflecting a paucity of high-quality randomised studies in this area. Three major reviews advocate an opiate as the drug of choice for neonatal opiate withdrawal.^{20–22} A survey of practice in the United Kingdom (UK) in 1994²³ highlighted that chlorpromazine was the agent most commonly utilised (70.8%), with opioids used in 10.8% of units. The purpose of our current manuscript is to present the results of the most comprehensive appraisal to date pertaining to management of NAS in the UK and Ireland.

METHODS

A postal questionnaire was administered to a consultant paediatrician or neonatologist in each of 235 neonatal units in the UK and Republic of Ireland in April 2008. Non-respondents were followed up and a telephone interview was conducted by the chief investigators. Neonatal centres in England, Scotland, Wales and Northern Ireland were identified from the 2008 edition of the *Directory of Critical Care* (CMA Medical Data),

while the 2006–2007 edition of the *Irish Medical Directory* was consulted with regard to units in the Republic of Ireland.

Data sought included number of infants treated, abstinence scoring system used, policy on toxicology testing, and pharmacological management of opiate and polysubstance abuse including seizures, should they occur. Policies regarding discharge of infants on medication, breastfeeding and use of cranial ultrasound were also explored (appendix A). Data were entered on a Microsoft Excel spreadsheet (Microsoft, Redmond, WA), and descriptive statistics including the mean, median and frequency were calculated. Data analysis was performed using StatsDirect v 2.7.2. Categorical variables were compared using the χ^2 analysis.

RESULTS

Of the 235 questionnaires distributed, completed responses were obtained from 211 neonatal units (90%). Overall, 198 (94%) units were responsible for the routine postnatal care of infants of drug-addicted women, and of these 190 (96%) had a formal guideline. The median number of infants treated for neonatal abstinence annually was 6 (range 1–100). Seventy one per cent of respondents had used pharmacological management for NAS on 10 or less occasions in the preceding 12-month period and 70% of clinicians routinely collect urine for toxicology on all withdrawing newborns prior to initiation of treatment.

When deciding when to initiate, intensify or moderate treatment, 191 (96.5%) centres utilise an objective scoring system. The most frequently used method was that described by Finnegan (52%). The chart either in its original or its modified form was used significantly more frequently in the Republic of Ireland than in the UK (93% vs 48%, $p < 0.001$). The threshold for initiation of drug therapy in 49% of units was a score ≥ 8 , while in 22% of units the treatment threshold was lower. The Lipsitz tool advocated by the American Academy of Pediatrics (AAP), and the Liverpool (Mc Allister and Gregg) and Rivers charts were used to a similar extent (7%, 7% and 6%, respectively). Twelve per cent of units had developed their own scoring system and a further 10% were uncertain of the origin of the chart applied to their population.

Pharmacological agents used in the management of NAS secondary to opiate and polysubstance withdrawal are detailed in table 1. Morphine sulphate (92%) is the most commonly used

medication for the treatment of opiate withdrawal. The dosing schedule most frequently utilised was 40 $\mu\text{g}/\text{kg}$ 4 hourly (45%), with a further 9% of units using the same quantity 6 hourly. Twenty three different treatment regimes in total were reported, with doses ranging from 10 to 400 $\mu\text{g}/\text{kg}$ administered 2–8 hourly. The maximum dose used when intensifying treatment ranged from 40 $\mu\text{g}/\text{kg}$ to 1.3 mg/kg; however, one third of units increased the dose as required to control symptoms and thus did not have a specified upper limit. Thirty nine per cent of units did not require a second medication for opiate withdrawal. Centres whose maximum daily morphine dose was $< 400 \mu\text{g}/\text{kg}/\text{day}$ were significantly more likely to require an additional medication than those whose threshold was higher (76% vs 58%, $p = 0.027$). Phenobarbitone was the most frequently used second line agent for both opiate and polydrug withdrawal. However, its use as a first line therapy for opiate withdrawal was restricted to Ireland. Sixty two per cent of those using phenobarbitone administered a loading dose even in the absence of seizures. Fifty five per cent of clinicians elected to use a loading dose of 15 mg/kg, a quarter used 20 mg/kg and the remainder administered 10 mg/kg. Management of withdrawal seizures is outlined in table 2.

Infants with neonatal abstinence were allowed home on medications from 57 units (29%) (table 3). Eighty one per cent of units encourage mothers on methadone to breastfeed provided they are HIV negative and are stable on a low dose, while 7% were actively discouraging. Fifty three units (27%) discourage mothers from breastfeeding if their serology is positive for hepatitis B and/or hepatitis C. Almost a quarter of units routinely perform cranial ultrasounds on all withdrawing infants, while a similar number image infants exposed in utero to cocaine. Fifty five per cent of units have a drugs liaison midwife.

DISCUSSION

Our audit highlights significant alterations in practice in the 14-year period since 1994.²³ Approximately 94% of units now use an opioid (morphine or methadone) as recommended^{20–22} and this compares favourably with 83% of a recently published American cohort.²⁴ Dosing regimens varied widely, and less than half of the units surveyed in our study used an initial morphine sulphate dose of 40 $\mu\text{g}/\text{kg}$ 4 hourly, which is the dose recommended in the *British National Formulary for children 2008*. An interesting observation of our study was that units that use a maximum daily dose of $< 400 \mu\text{g}/\text{kg}/\text{day}$ in divided doses, were significantly more likely to require the addition of a second drug. A randomised controlled trial is needed to confirm or refute these findings. We did not endeavour to collect length of treatment or length of stay data as we considered it unlikely that the majority of units would be able to provide such information readily, in the absence of a recent internal audit. Comparison of drug dosing regimens, numbers of infants treated and length of stay data should be addressed as the principal focus for future studies to address questions such as: (1) Is under-dosing with opiates clinically disadvantageous? and (2) Do larger more experienced units provide more efficient care?

Chlorpromazine is no longer used as the treatment of choice for neonatal opiate withdrawal but retains a role as an adjunctive treatment in 11.6% of units in our audit. A recent retrospective review²⁵ concluded that the duration of treatment required is shorter with chlorpromazine than morphine; however, compared with opiates, infants treated with

Table 1 Pharmacological agents used in the management of neonatal abstinence syndrome following in utero opioid or polydrug exposure

1st line opiate withdrawal		2nd line opiate withdrawal	
Morphine sulphate	182 (92.0%)	None required	77 (39.0%)
Phenobarbitone	7 (3.5%)	Phenobarbitone	47 (23.7%)
Chloral hydrate	5 (2.5%)	Chloral hydrate	31 (15.7%)
Methadone	3 (1.5%)	Chlorpromazine	23 (11.6%)
Diazepam	1 (0.5%)	Morphine sulphate	11 (5.5%)
		Benzodiazepine	6 (3.0%)
		Methadone	3 (1.5%)
1st line polydrug exposure		2nd line polydrug exposure	
Morphine sulphate	137 (69.0%)	None required	50 (25.3%)
Phenobarbitone	28 (14.0%)	Phenobarbitone	37 (18.7%)
Chloral hydrate	9 (4.5%)	Chloral hydrate	23 (11.6%)
Methadone	4 (2.0%)	Chlorpromazine	18 (9.1%)
Chlorpromazine	3 (1.5%)	Benzodiazepines	7 (3.5%)
Diazepam	2 (1.0%)	Unanswered	49 (24.7%)
Variable	15 (8.0%)		

Table 2 Management of opiate and polydrug withdrawal seizures

1st line opiate withdrawal seizures		1st line polydrug withdrawal seizures	
Phenobarbitone	128 (73%)	Phenobarbitone	134 (81%)
Morphine	33 (19%)	Morphine	14 (9%)
Benzodiazepines	4 (2%)	Benzodiazepine	7 (4%)
Phenytoin	2 (1%)	Phenytoin	3 (2%)
Methadone	2 (1%)	Methadone	2 (1%)
Combination therapy	7 (4%)	Combination therapy	5 (3%)

chlorpromazine appear more likely to develop seizures.²⁶ A Cochrane review concluded there was no role for chlorpromazine in NAS due to a lack of randomised studies.²⁷ Similarly, chloral hydrate which exerts a sedative effect through the metabolite trichloroethanol is utilised in approximately 18% of units despite a lack of evidence to support such a policy. An adverse gastrointestinal side-effect profile further limits its usefulness. Chlorpromazine and chloral hydrate employed for the management of NAS need to be assessed in the setting of a randomised trial before further recommendations can be made.

Phenobarbitone (23.8%) was the most commonly used combination therapy with morphine for opiate withdrawal in our study. Coyle *et al*,²⁸ in a small partially randomised study of 20 patients, demonstrated a 48% reduction in length of stay with an opiate (diluted tincture of opium, DTO) and phenobarbitone compared to DTO alone; however, the mean length of stay in the DTO group was 79 days. Sixty two per cent of neonatologists in our study administer a loading dose when using phenobarbitone for opiate or polydrug withdrawal. Nonetheless, evidence is conflicting from trials on whether or not a loading dose influences treatment outcomes.^{29–30} Phenobarbitone was the anticonvulsant of choice for both opiate (73%) and polydrug (81%) withdrawal seizures. In a randomised comparison to infants treated for NAS with opiates, seizures were more prevalent in those administered phenobarbitone.³¹

Seventy per cent of respondents routinely collect urine for toxicology on all withdrawing newborns prior to initiation of treatment. It has been suggested elsewhere that maternal rather than neonatal urine should be collected as there is a stronger correlation between maternal urine toxicology and neonatal withdrawal.³² Meconium testing was almost non-existent in our cohort. It has, however, been demonstrated to be superior to urine testing in terms of detection rate, profiling of drug exposure over a longer period of gestation and ease of sample collection.³³ Technical aspects, however, preclude its use outside of specialised laboratories.

The observation that 29% of respondents allow infants to be discharged home on medication was a surprising one. Furthermore, 58% of these units allowed administration of either morphine or methadone in the community and in almost half of cases this was managed by a parent. Data concerning the safety of such a practice are limited. One small retrospective review of 22 infants who were administered morphine for NAS in the community by their parents reported no major adverse events.³⁴ A high intensity follow-up with frequent telephone calls and once or twice weekly home visits in addition to weekly outpatient clinic attendances was required. Furthermore, no information regarding the social environment to which the child was being discharged was reported, thus limiting the applicability of this practice. Considering that high prevalence areas such as that served by the Glasgow Royal Maternity Hospital have seen a 10-fold increase in neonatal abstinence over the past decade and a prolonged length of stay is sometimes required,¹⁶

Table 3 Medications allowed on discharge

Discharge medications, n = 62 (57 units)	n (%)
Morphine (foster parents/community midwife)	17 (27.5)
Morphine (parent)	17 (27.5)
Phenobarbitone	17 (27.5)
Chlorpromazine	5 (8)
Chloral hydrate	4 (6.5)
Methadone (foster parents/community midwife)	2 (3)

the safety and feasibility of NAS management in the community merits further study, with particular attention to safety and the resources required.

Our survey revealed that 81% of units encourage HIV negative women on methadone to breastfeed, although some specified that they should be stable on a low dose. The concentration of methadone in breast milk is low and does not correlate with maternal dose.³⁵ Breastfed infants of women on methadone have lower Finnegan scores and reduced need for pharmacotherapy compared to their formula-fed counterparts.³⁶ Seven per cent of units actively discouraged breastfeeding; trepidation that abrupt cessation may precipitate withdrawal may be a contributory factor.³⁷ Breastfeeding guidelines from the American Academy of Pediatrics state that methadone is “usually compatible with breastfeeding”, benzodiazepines are of “unknown effect but may be harmful”, phenobarbitone has “significant effects documented - use with caution” and contraindicate amphetamines, cocaine, heroin, marijuana and phencyclidine as harmful effects have been documented in nursing infants.³⁸

In contrast, four times as many units (27%) discourage breastfeeding if the maternal serology is positive for hepatitis B and/or C. Breastfeeding is contraindicated in HIV positive women in developed countries due to the risk of vertical transmission via this route. Seropositivity for hepatitis B and/or C is, however, not a contraindication³⁹ provided the infant is vaccinated and given hepatitis B immunoglobulin as soon as possible after delivery. The discordant findings of our study may reflect a lack of awareness of current guidelines; however, a concern that the hyperphagic and frequently poorly coordinated feeding pattern of such infants may result in cracked or bleeding nipples with resultant blood-borne exposure seems plausible. This could be addressed by promoting the use of nipple shields, or expressing milk should such concerns exist.

In summary, our study highlights widespread variation in practices with regard to the management of NAS. This reflects the paucity of high quality randomised trials in the area, which is responsible to a certain extent for the prevalence of non-evidence based treatments in current use. Quite a significant alteration in practice has occurred since practice was last audited in 1994 and the authors would recommend re-evaluating at regular intervals of not greater than 5 years, particularly to assess changes in response to developments in the published literature. Similarly, we would also advocate that each unit evaluates its own practice, so that such data can be gathered and collated in future studies similar to ours. Useful information concerning the demographics of local drug misuse, length of stay, treatment in the community and long-term neurodevelopmental outcome could also be ascertained using this method.

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APPENDIX A

Survey of current practice in managing neonatal abstinence syndrome

1. Do you treat infants with neonatal abstinence syndrome (NAS) in your unit? (tick)
YES **NO** → If YES, state approx. number treated annually _____

If YES, does your unit have a written policy/protocol for management of such infants?
YES **NO**

2. Which scoring system do you use for infants with NAS?

FINNEGAN OTHER (specify) _____

3. What criteria do you use for starting pharmacologic therapy?

SCORE ≥ _____ OTHER (specify) _____

4. Toxicology testing is carried out on (tick)?

URINE MECONIUM Results available within _____ days

Do you inform the mother before toxicology testing? **YES** **NO**

5. What is the 1st line agent used by you for opiate induced NAS?

A. Dose & Frequency? _____

B. Is the dose score based? **YES** **NO**

C. Maximum dose? _____

D. Method of weaning? _____

6. What is the 2nd line agent used for opiate induced NAS? _____

A. Dose & Frequency? _____

B. Maximum dose? _____

C. Method of weaning? _____

7. What is the first line agent used for polysubstance induced NAS? _____

A. Dose & Frequency? _____

B. Maximum dose? _____

C. Method of weaning? _____

8. What is the 2nd line agent used for polysubstance induced NAS? _____

Dose & Frequency? _____

B. Maximum dose? _____

C. Method of weaning? _____

9. Do infants with NAS have to be off medications prior to discharge? **YES** **NO**

What medications (if any) do you allow infants to be discharged home on? (Specify) _____

10. Do you designate a person other than the parent(s) to administer medications at home?

YES **NO** **DEPENDS** (specify) _____

11. What agent do you use as first line for management of seizures in...

Infants of mothers on opiates alone _____

Infants of mothers with polysubstance use _____

12. What is your policy on breastfeeding in mothers who are

a) on methadone **ENCOURAGE** **DISCOURAGE**

b) Hepatitis B and/or C positive **ENCOURAGE** **DISCOURAGE**

13. Do you routinely perform cranial ultrasound on infants of mothers who use opiates and/or other substances while pregnant

ALL **NONE** **SOME** (Specify) _____

14. What post discharge follow-up do these infants receive? (Specify) _____

15. Do you have a drug liaison midwife available to you?

YES **NO**