

REVIEW

Treatment of neonatal abstinence syndrome

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Neonatal abstinence syndrome (NAS) is suffered by infants withdrawing from substances on which they have become physically dependent after in utero exposure. They may require prolonged treatment and spend weeks or even months in hospital. A wide range of drugs have been used to treat NAS. The efficacy of few, however, have been adequately investigated. Evidence suggests that opioids are the most appropriate, at least in infants exposed to diamorphine or methadone. In all "head to head" trials, diazepam has been shown to be ineffective. Morphine and methadone are currently the most commonly prescribed opioids to treat NAS, but randomised trials have not been undertaken to determine which is the more beneficial. Many infants with NAS have been exposed to multiple substances in utero. Further research is required into whether a single opiate or a multiple drug regimen is the best option for such patients.

cry, tremors, hypertonicity, vomiting, diarrhoea, and tachypnoea.

Diamorphine used to be the most common opiate abused in pregnancy, but now it is methadone.⁶ Women enrolled in methadone programmes have been reported to have better antenatal care than those not in such programmes,^{7–9} but methadone rather than diamorphine can cause more severe and prolonged withdrawal in infants with NAS.^{8–10} NAS is often used to describe neonatal opiate withdrawal, but the use of other illicit substances may contribute to the neonate's ill health. Benzodiazepine use can result in withdrawal requiring treatment, and, in one series,¹¹ 50% of pregnant women abusing opiates were also taking benzodiazepines. Barbiturate use (prescribed and illicit) during pregnancy can also result in withdrawal symptoms sufficiently severe to require treatment.^{12–13} One third of methadone users have been reported to take cocaine,¹⁴ which is known to have significant vasoconstrictive effects on the developing brain,¹⁵ leading to neurological abnormalities.^{16–17} Cocaine use alone does not cause NAS; abstinence scores, however, were significantly higher in infants exposed to both cocaine and diamorphine than in those exposed to diamorphine alone.¹⁸

Between 30%¹⁹ and 80%²⁰ of infants exposed to opiates in utero require treatment for NAS.²⁰ Many agents have been used including a variety of opioids, clonidine, chloral hydrate, chlorpromazine, diazepam, and phenobarbitone. A survey of UK practice in 1994²¹ highlighted chlorpromazine as the most commonly prescribed agent, being administered in 70.8% of neonatal units that had prescribing recommendations or policies. Opioids (morphine, methadone, or diamorphine) were prescribed in 10.8% of units, and phenobarbitone and chloral hydrate in 9.2% and 7.7% respectively. Additional agents, most commonly phenobarbitone and morphine, were used, when required in about 50% of those units. The aim of this review was, by examining the available evidence, to determine whether it was possible to identify the most appropriate treatment for infants suffering from NAS.

PHARMACOLOGICAL ACTIONS OF TREATMENTS USED FOR NAS

Morphine, diamorphine, and methadone activate opiate receptors in the locus ceruleus, one of the major clusters of noradrenergic cells in the brain. Their action decreases the activity of adenylate cyclase, resulting in a reduction in cAMP production.^{22–23} As a consequence, potassium efflux is increased and calcium influx into the cell is decreased, resulting in a decrease in noradrenaline (norepinephrine) release.²⁴ During chronic opiate use, noradrenaline release gradually increases towards its normal level as tolerance

Misuse of a wide variety of substances during pregnancy is common. Anonymous screening of women attending antenatal clinics showed that 11–16% were taking at least one illicit substance^{1–2} (table 1). Most women were taking cannabis alone, but this substance may have adverse effects on fetal wellbeing.³ In utero exposure to cannabis has been associated with delivery at a significantly earlier gestation and a reduction in birth weight.³ The effect on birth weight, however, appears to be less than that resulting from in utero tobacco exposure. Smoking during pregnancy has been associated with a mean reduction in birth weight of 256 g,³ whereas meta-analysis of studies examining the effects of cannabis exposure has highlighted that the mean reduction in birth weight in infants of frequent users (at least four times a week) was only 131 g.⁴ It is essential to screen all antenatal women, to obtain an accurate incidence of drug use during pregnancy, as, in one study,⁵ nearly 40% of pregnant women screened who had positive urine tests for non-prescribed substances denied drug misuse. There are, however, important ethical issues in universal screening that must be considered before adopting such an approach. Infants exposed to certain drugs in utero may become physically dependent on them and after birth suffer withdrawal symptoms, termed the neonatal abstinence syndrome (NAS). NAS is characterised by central nervous system, gastrointestinal, and respiratory dysfunction. Affected infants commonly have irritability, high pitched

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Table 1 Illicit substance use in women attending two inner city London antenatal clinics

	Farkas <i>et al</i> ¹	Sherwood <i>et al</i> ²
Number screened	1000	807
Cannabis	8.5	14.5
Opiates (including methadone)	1.7	1.4
Cocaine	1.1	0.4
One or more illicit substances	10.6	15.6

Data are expressed as the percentage of the population in which the substances were detected.

develops.²⁵ Once the opiates are withdrawn, there is loss of the inhibitory effect, and a significant increase in noradrenaline release to well above normal levels.²⁶ This increase in noradrenergic activity coincides with the appearance of withdrawal symptoms in experimental models.²⁷ Administration of opioids results in a reduction in neuronal activity and hence a decrease in withdrawal symptoms. Methadone and morphine have cross dependence and similar receptor effects. There are, however, potential advantages of methadone over morphine. These include better oral bioavailability, as morphine has extensive first pass metabolism, and a longer duration of action.^{25 28 29} Clonidine also has inhibitory effects on noradrenaline release in the locus ceruleus, as it is an α_2 adrenoceptor agonist. Rats treated with clonidine before the induction of opiate withdrawal had less severe withdrawal signs.²⁶

Sedative agents such as chloral hydrate, chlorpromazine, diazepam, and phenobarbitone have also been used to treat infants with NAS. They act non-specifically to reduce the manifestations of NAS. Chloral hydrate exerts a hypnotic effect through its active metabolite trichloroethanol. Although some neonatologists have used chloral hydrate as a first line treatment for NAS infants,²¹ there is no published evidence to support such a policy. Chlorpromazine is a neuroleptic which acts on the hypothalamus and brainstem. Benzodiazepines have a variety of effects, but in NAS they are given for their sedative action, which results from binding to the inhibitory γ aminobutyric acid (GABA) receptor complex in the brain.^{25 28 29} Phenobarbitone is a central nervous system depressant and also acts on the GABA receptor complex, but it has a less specific effect on the brain than diazepam.^{25 28 29}

CLINICAL EVIDENCE

Anecdotal series

Control of symptoms was reported in six of the seven infants treated with clonidine exposed to methadone antenatally, and no toxic effects were observed.³⁰ Retrospective comparison of those infants with a cohort treated with phenobarbitone showed that the length of treatment was significantly shorter in the clonidine treated group. Diazepam administration controlled symptoms within 72 hours without any reported adverse effects in 18 infants who had been exposed in utero to diamorphine.³¹

Placebo controlled trials

There are none.

Treatment comparison

Non-randomised and randomised comparison trials have been undertaken, but the method of randomisation has not been described in any of the studies (table 2). A variety of outcome measures have been used.

Sucking

The impact of treatment on sucking has been investigated in three non-randomised trials.³²⁻³⁴ Sucking rate is depressed in infants of drug dependent mothers; this effect is more pronounced in infants exposed antenatally to methadone.³⁴ Paregoric (an opiate preparation) was reported to be more

effective than either phenobarbitone or diazepam in restoring a normal sucking pattern.³²⁻³⁴ Treatment with diazepam resulted in a sucking pattern that was less effective than that seen in untreated NAS infants.

Seizures

The results of a non-randomised study which included 56 withdrawing infants suggested that chlorpromazine was less efficacious in controlling seizures than methadone; 14 of the 44 infants treated with chlorpromazine developed seizures compared with none of the 12 treated with methadone.³⁵ Other non-randomised trials have suggested that paregoric³⁶ and tincture of opium⁸ may be more effective than diazepam in preventing seizures associated with NAS.³⁶ Only one randomised study examining which treatment most effectively controlled seizures in NAS has been reported; paregoric was more effective than phenobarbitone.³⁷

Control of NAS symptoms

In a non-randomised trial, morphine was found to be more effective than combined treatment with phenobarbitone and diazepam.³⁸ Chlorpromazine and phenobarbitone may have similar efficacy in controlling symptoms,³⁹ as no statistically significant difference in tremor and irritability, assessed by clinical observation, was found between two groups of infants so treated. Symptom control and the influence of treatment on longer term development has only been addressed in one randomised trial, in which the efficacy of paregoric, phenobarbitone, and diazepam were compared.⁴⁰ Paregoric was found to be the most effective agent: all the infants who received diazepam and approximately half of those who received phenobarbitone required a second agent to control their symptoms. No difference, however, was found at six months in the Bayley scale of mental development score between the three groups.⁴⁰

Duration of treatment

Two randomised studies have been undertaken. In one,⁴¹ phenobarbitone was associated with a shorter duration of treatment than paregoric, in the other⁴² there were no statistically significant differences in treatment duration between infants prescribed methadone, phenobarbitone, or diazepam.

TREATMENT OF INFANTS WITH POLYDRUG EXPOSURE

Paregoric was shown to be more effective than phenobarbitone or diazepam in controlling symptoms in opiate exposed infants in two randomised trials.^{43 44} In both those trials, however, phenobarbitone was the most effective treatment for infants exposed to polydrugs.^{43 44} The results of a recently published study⁴⁵ suggest that a combination of agents may be better treatment for the NAS suffered by infants exposed to multiple drugs in utero. Phenobarbitone given with diluted tincture of opium compared with diluted tincture of opium alone was associated with a shorter hospital stay required for NAS treatment, and hence the hospital cost per patient was reduced by \$35 000. The study, however, was only partially randomised, and the total sample examined was 20.

ADVERSE EFFECTS OF DRUGS USED TO TREAT NAS

Side effects of opioids include respiratory depression, which results from a decrease in the sensitivity of brainstem chemoreceptors to carbon dioxide (CO₂).^{28 29} In a randomised study⁴⁶ in which morphine, methadone, and pethidine were compared in children requiring pain relief after an operation, although no patient developed apnoea or hypoventilation that required intervention, methadone administration was associated with the greatest increase in end tidal CO₂. In utero exposure to diamorphine is less likely to result in respiratory depression; indeed affected infants have been noted to have increased

Table 2 Treatment comparison trials

Reference	Type of drug exposure in utero	No of infants examined	Treatments	Randomisation	Outcome measure	Results
Kron <i>et al</i> ³⁴	Methadone	26	Paregoric/ phenobarbitone/ diazepam	Not stated whether randomised	Sucking	Average sucking rate 31.1 sucks/min in paregoric group, 19.9 sucks/min in phenobarbitone group ($p<0.05$), and 39.6 sucks/min in control infants. Sucking rate 6.5 sucks/min in diazepam group versus 23.8 sucks/min in the controls
Finnegan <i>et al</i> ³²	Methadone	38	Paregoric/ phenobarbitone	Not randomised	Sucking	Average sucking rate 29.0 sucks/min in the paregoric treated, 24.1 sucks/min in the phenobarbitone treated infants
Kron <i>et al</i> ³³	Diamorphine/ methadone	42	Paregoric/ phenobarbitone/ diazepam	Not stated whether randomised	Sucking	Average sucking rate 30.5 sucks/min in the paregoric group (n=5), 19.4 sucks/min in the phenobarbitone group (n=28), 18.4 sucks/min in the diazepam group (n=6), and 23.2 in the controls (n=8)
Herzlinger <i>et al</i> ³⁶	Diamorphine/ methadone	65	Paregoric/diazepam	Not randomised	Seizures	Two of 48 paregoric treated infants and 5 of 12 diazepam treated infants had seizures ($p<0.01$)
Kandall <i>et al</i> ³⁸	Diamorphine/ methadone	132	Tincture of opium/diazepam	Not stated	Seizures	More convulsions seen in infants treated with diazepam ($p<0.01$)
Kandall <i>et al</i> ³⁸	Methadone	111	Paregoric/ phenobarbitone	Randomisation method not stated	Seizures	No infant had seizures in the paregoric group, 7 of 62 infants in the phenobarbitone group had seizures ($p<0.025$)
Pacifico <i>et al</i> ³⁷	Diamorphine	25	Morphine/ phenobarbitone + diazepam/morphine + phenobarbitone + diazepam	Not stated	Symptom control	Maximum withdrawal score 35 in the morphine treated group, 75 in the phenobarbitone + diazepam group and 100 in the phenobarbitone + diazepam + morphine group
Kahn <i>et al</i> ³⁹	Diamorphine	38	Phenobarbitone/ chlorpromazine	Randomisation method not stated	Symptom control	There was no significant difference in symptom control, as assessed by clinical observation in the 19 infants treated with chlorpromazine and the 19 treated with phenobarbitone
Finnegan <i>et al</i> ⁴⁴	Opiate/polydrug	139	Paregoric/ phenobarbitone/ diazepam	Randomisation method not stated	Symptom control	Opiate exposed group; treatment success (as assessed by no need for a second therapeutic agent) 13 of 14 paregoric treated, 13 of 26 phenobarbitone treated and 0 of 5 diazepam treated infants. Polydrug exposed group, treatment success; 11 of 18 paregoric treated, 54 of 61 phenobarbitone treated and 6 of 9 diazepam treated infants
Finnegan and Ehrlich ⁴³	Opiate/polydrug	300	Paregoric/ phenobarbitone/ diazepam	Randomisation method not stated	Days to symptom control	Opiate exposed infants, mean days to symptom control 4.9 in paregoric treated, 6.7 in phenobarbitone treated and 9.5 in diazepam treated infants. Polydrug exposed: 3.5 days in the phenobarbitone treated, 4.7 in the diazepam treated and 7 in the paregoric treated infants
Kaltenbach and Finnegan ⁴⁰	Methadone	69	Paregoric/ phenobarbitone/ diazepam	Randomisation method not stated	Symptom control Developmental outcome at 6 months	2 of 23 paregoric treated, 11 of 20 phenobarbitone treated and 10 of 10 diazepam treated infants required a second agent to control symptoms. No significant difference in the developmental outcome at 6 months of the three groups
Madden <i>et al</i> ⁴²	Diamorphine/ methadone	50	Methadone/ phenobarbitone/ diazepam	Randomisation method not stated	Duration of treatment	Mean treatment duration: 11.7 days in methadone treated, 14.5 days in phenobarbitone treated and 10.2 days in diazepam treated infants
Carin <i>et al</i> ⁴¹	Methadone	31	Paregoric/ phenobarbitone	Randomisation method not stated	Duration of treatment	Mean duration of treatment: 22 days in phenobarbitone treated infants, 17 days in paregoric treated infants ($p<0.01$)

respiratory rates and become hypocarbic.⁴⁷ In addition, prematurely born infants of diamorphine addicted mothers have less respiratory distress syndrome,⁴⁸ which may be explained by accelerated lung maturation.⁴⁹ Opioids can often induce nausea and vomiting, as a result of stimulation of the chemoreceptor trigger zone in the medulla. The use of paregoric is no longer recommended because of the potentially toxic additive substances it contains; these include camphor, ethanol, benzoic acid, and anise oil. Adverse effects of clonidine relate to its α agonist action, which reduces noradrenaline release, leading to a reduction in sympathetic outflow and reduced peripheral resistance, heart rate, cardiac output, and blood pressure. The major adverse effect of chloral hydrate is gastrointestinal irrita-

tion. Chlorpromazine use may result in cerebellar dysfunction and haematological problems.⁵⁰ Concerns have been raised about the safety of diazepam use in neonates. The intravenous preparation, which has been given orally in the treatment of NAS,³¹ contains a significant amount of sodium benzoate, a potent bilirubin-albumin uncoupler.⁵¹ Neonates may also have a poor ability to metabolise and excrete diazepam.⁵² Other adverse effects of diazepam include respiratory depression, hypotonia, reluctance to feed, and an impaired metabolic response to a cold stress.⁵³ Withdrawal from diazepam is associated with jitteriness and hypertonia, and, although diazepam will stop most neonatal seizures at least briefly, the drug's anticonvulsant effect is poorly sustained. Phenobarbitone has a low therapeutic

index, as a consequence it has been recommended that levels should be measured during treatment.⁵⁰ Infants may be excessively sleepy and feed poorly. Other potential disadvantages of phenobarbitone include induction of liver enzymes and a rapid tolerance to its sedative effect.⁵⁰

CONCLUSION

"The limited evidence available suggests that opioids are the most effective treatment in controlling acute problems related to NAS from in utero opioid exposure"

Few appropriately designed trials have been undertaken to determine the most appropriate treatment for infants suffering from NAS. The limited evidence available suggests that opioids are the most effective treatment in controlling acute problems related to NAS from in utero opioid exposure. Increasingly, however, infants have polydrug exposure, and there is little information on how to treat such patients. Infants with NAS may require months of treatment and suffer problems after discharge. Randomised trials are required to determine which treatment for infants with NAS is associated with the best short and long term outcomes.

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