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.

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 (table 1). Most women were taking cannabis alone, but this substance may have adverse effects on fetal wellbeing. In utero exposure to cannabis has been associated with delivery at a significantly earlier gestation and a reduction in birth weight. 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, 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. It is essential to screen all antenatal women to obtain an accurate incidence of drug use during pregnancy, as, in one study, 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 cry, tremors, hypertonicity, vomiting, diarrhoea, and tachypnoea.

Diamorphine used to be the most common opiate abused in pregnancy, but now it is methadone. Women enrolled in methadone programmes have been reported to have better antenatal care than those not in such programmes, but methadone rather than diamorphine can cause more severe and prolonged withdrawal in infants with NAS. 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, 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. One third of methadone users have been reported to take cocaine, which is known to have significant vasoconstrictive effects on the developing brain, leading to neurological abnormalities. 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. Between 30% and 80% of infants exposed to opiates in utero require treatment for NAS. Many agents have been used including a variety of opioids, clonidine, chloral hydrate, clonpropazine, diazepam, and phenobarbitone. A survey of UK practice in 1994 highlighted clonpropazine 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. As a consequence, potassium efflux is increased and calcium influx into the cell is decreased, resulting in a decrease in noradrenaline (norepinephrine) release. During chronic opiate use, noradrenaline release gradually increases towards its normal level as tolerance
noradrenergic activity coincides with the appearance of with-  
opiate withdrawal had less severe withdrawal signs.  
action.  
extensive first pass metabolism, and a longer duration of  
These include better oral bioavailability, as morphine has  
decrease in withdrawal symptoms. Methadone and morphine  
opioids results in a reduction in neuronal activity and hence a  
develops.22 Once the opiates are withdrawn, there is loss of the  
inhibitory effect, and a significant increase in noradrenaline  
release to well above normal levels.23 This increase in  
noradrenergic activity coincides with the appearance of with-  
drawal symptoms in experimental models.24 Administration of  
opioids results in a reduction in neural activity and hence a  
decrease in withdrawal symptoms. Methadone and morphine  
have more 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 26 27 Clonidine also has inhibitory effects on noradren-  
aline release in the locus ceruleus, as it is an α2 adrenoceptor  
agonist. Rats treated with clonidine before the induction of  
opiate withdrawal had less severe withdrawal signs.28  
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 an hypnotic  
effect through its active metabolite trichloroethanol. Although  
some neonatologists have used chloral hydrate as a first line  
treatment for NAS infants,29 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 26 27  
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 26 27  

**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 out-  
come measures have been used.

**Sucking**  
The impact of treatment on sucking has been investigated in  
three non-randomised trials.32 33 34 Sucking rate is depressed in  
infants of drug dependent mothers; this effect is more  
pronounced in infants exposed antenatally to methadone.33  
Paregoric (an opiate preparation) was reported to be more  
effective than either phenobarbitone or diazepam in restoring  
a normal sucking pattern.34 35 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  
drawing 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.36  
Other non-randomised trials have suggested that paregoric37  
and tincture of opium3 may be more effective than diazepam  
in preventing seizures associated with NAS.38 Only one  
randomised study examining which treatment most effec-  
tively controlled seizures in NAS has been reported; paregoric  
was more effective than phenobarbitone.39

**Control of NAS symptoms**  
In a non-randomised trial, morphine was found to be more  
effective than combined treatment with phenobarbitone and  
diazepam.40 Chlorpromazine and phenobarbitone may have  
similar efficacy in controlling symptoms,41 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, phenobar-  
bitone, and diazepam were compared.42 Paregoric was found to  
be the most effective agent: all the infants who received  
diazepam and approximately half of those who received pheno-  
barbitone 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.43

**Duration of treatment**  
Two randomised studies have been undertaken. In one,44  
phenobarbitone was associated with a shorter duration of  
treatment than paregoric, in the other43 there were no statisti- 
cally 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 phenobarbi-  
tone or diazepam in controlling symptoms in opiate exposed  
infects in two randomised trials.45 46 In both those trials, how- 
ever, phenobarbitone was the most effective treatment for  
infants exposed to polydrugs.45 46 The results of a recently pub- 
lished study47 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 chemo- 
receptors to carbon dioxide (CO2).48 49 In a randomised study50  
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  
treatment, 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 1 Illicit substance use in women attending two inner city London antenatal clinics

<table>
<thead>
<tr>
<th>Substance</th>
<th>Farkas et al40</th>
<th>Sherwood et al41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number screened</td>
<td>1000</td>
<td>807</td>
</tr>
<tr>
<td>Cannabis</td>
<td>8.5</td>
<td>14.5</td>
</tr>
<tr>
<td>Opiates (including methadone)</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>One or more illicit substances</td>
<td>10.6</td>
<td>15.6</td>
</tr>
</tbody>
</table>

Data are expressed as the percentage of the population in which the substances were detected.
respiratory rates and become hypocarbic.\textsuperscript{61} In addition, prema-
turely born infants of diamorphine addicted mothers have less
respiratory distress syndrome,\textsuperscript{62} truly born infants of diamorphine addicted mothers have less
accelerated lung maturation.

acid, and anise oil. Adverse effects of clonidine relate to its
stances it contains; these include camphor, ethanol, benzoic
acid, and haematological problems.

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Table 2  Treatment comparison trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of drug exposure in utero</th>
<th>No of infants examined</th>
<th>Treatments</th>
<th>Randomisation</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kron et al\textsuperscript{42}</td>
<td>Methadone</td>
<td>26</td>
<td>Pregoric/phenobarbitone/diazepam</td>
<td>Not stated whether randomised</td>
<td>Sucking</td>
<td>Average sucking rate 31.1 sucks/min in paregoric group, 19.9 sucks/min in phenobarbitone group (p&lt;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</td>
</tr>
<tr>
<td>Finnegan et al\textsuperscript{42}</td>
<td>Methadone</td>
<td>38</td>
<td>Pregoric/phenobarbitone</td>
<td>Not randomised</td>
<td>Sucking</td>
<td>Average sucking rate 29.0 sucks/min in the paregoric treated, 24.1 sucks/min in the phenobarbitone treated infants</td>
</tr>
<tr>
<td>Kron et al\textsuperscript{42}</td>
<td>Diamorphine/methadone</td>
<td>42</td>
<td>Pregoric/phenobarbitone/diazepam</td>
<td>Not stated whether randomised</td>
<td>Sucking</td>
<td>Average sucking rate 30.5 sucks/min in the paregoric group (n=8), 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 (p=8)</td>
</tr>
<tr>
<td>Herzlinger et al\textsuperscript{42}</td>
<td>Diamorphine/methadone</td>
<td>65</td>
<td>Pregoric/diazepam</td>
<td>Not randomised</td>
<td>Seizures</td>
<td>Two of 48 paregoric treated infants and 5 of 12 diazepam treated infants had seizures (p=0.01)</td>
</tr>
<tr>
<td>Madden et al\textsuperscript{42}</td>
<td>Diamorphine/methadone</td>
<td>111</td>
<td>Pregoric/phenobarbitone</td>
<td>Randomisation method not stated</td>
<td>Seizures</td>
<td>No infant had seizures in the paregoric group, 7 of 62 infants in the phenobarbitone group had seizures (p&lt;0.025)</td>
</tr>
<tr>
<td>Finnegan and Ehrlich\textsuperscript{42}</td>
<td>Opiate/polydrug</td>
<td>139</td>
<td>Pregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Symptom control</td>
<td>Maximum withdrawal score 35 in the morphine treated group, 75 in the phenobarbitone + diazepam group and 100 in the phenobarbitone+ diazepam + morphine group</td>
</tr>
<tr>
<td>Finnegann et al\textsuperscript{42}</td>
<td>Opiate/polydrug</td>
<td>300</td>
<td>Pregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Days to symptom control</td>
<td>Opine exposed infants, mean days to symptom control 4.9 in paregoric treated, 6.7 in phenobarbitone treated and 9.5 in diazepam treated infants</td>
</tr>
<tr>
<td>Kaltenbach and Finnegan\textsuperscript{42}</td>
<td>Methadone</td>
<td>69</td>
<td>Pregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Developmental outcome at 6 months</td>
<td>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</td>
</tr>
<tr>
<td>Madden et al\textsuperscript{42}</td>
<td>Diamorphine/methadone</td>
<td>50</td>
<td>Methadone/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Duration of treatment</td>
<td>Mean treatment duration: 11.7 days in methadone treated, 14.5 days in phenobarbitone treated and 10.2 days in diazepam treated infants</td>
</tr>
<tr>
<td>Carin et al\textsuperscript{42}</td>
<td>Methadone</td>
<td>31</td>
<td>Pregoric/phenobarbitone</td>
<td>Randomisation method not stated</td>
<td>Duration of treatment</td>
<td>Mean duration of treatment: 22 days in phenobarbitone treated infants, 17 days in paregoric treated infants (p&lt;0.01)</td>
</tr>
</tbody>
</table>

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index, as a consequence it has been recommended that levels should be measured during treatment.\textsuperscript{49} Infants may be excessively sleepy and feed poorly. Other potential disadvantages of pharmacotherapy include induction of liver enzymes and a rapid tolerance to its sedative effect.\textsuperscript{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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**REFERENCES**


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