TREATMENTS USED FOR NAS

These treatments can also result in withdrawal symptoms sufficient to require 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, chlorpromazine, diazepam, and phenobarbitone. A survey of UK practice in 1994 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. 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 withdrawal had less severe withdrawal signs. Rats treated with clonidine before the induction of aline release in the locus ceruleus, as it is an action. These include better oral bioavailability, as morphine has extensive first pass metabolism, and a longer duration of action. Clonidine also has inhibitory effects on noradrenaline release in the locus ceruleus, as it is an α1 adrenergic agonist. Rats treated with clonidine before the induction of opiate withdrawal had less severe withdrawal signs. 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 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. Clonidine also has inhibitory effects on noradrenaline release in the locus ceruleus, as it is an α1 adrenergic agonist. Rats treated with clonidine before the induction of opiate withdrawal had less severe withdrawal signs.

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respiratory rates and become hypocarbic. In addition, prematurely born infants of diamorphine addicted mothers have less respiratory distress syndrome, which may be explained by accelerated lung maturation.

Inhalational treatments which may be used include chloral hydrate, chloral hydrate and phenobarbitone, chloral hydrate and morphone or a mixture of phenobarbitone and diazepam, and chlorpromazine. The main adverse effect of chloral hydrate is gastrointestinal irritation. Chlorpromazine use may result in cerebellar dysfunction and haematological problems. 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, contains a significant amount of sodium benzoate, a potent bilirubin-albumin uncoupler. Neonates may also have a poor ability to metabolise and excrete diazepam. Other adverse effects of diazepam include respiratory depression, hypotonia, and, although diazepam will stop most neonatal seizures as least briefly, the drug's anticonvulsant action, which reduces noradrenaline release, leading to a reduction in sympathetic outflow and resistance, heart rate, cardiac output, and blood pressure. The major adverse effect of chloral hydrate is gastrointestinal irritation.

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[^34]</td>
<td>Methadone</td>
<td>26</td>
<td>Paregoric/phenobarbitone/diazepam</td>
<td>Not stated</td>
<td>Sucking</td>
<td>Average sucking rate 31.1 sucks/min in paregoric group, 19.9 sacks/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[^30]</td>
<td>Methadone</td>
<td>38</td>
<td>Paregoric/phenobarbitone</td>
<td>Not randomised</td>
<td>Sucking</td>
<td>Average sucking rate 29.0 sucks/min in the paregoric, 24.1 sucks/min in the phenobarbitone treated infants.</td>
</tr>
<tr>
<td>Kron et al[^32]</td>
<td>Diamorphine/methadone</td>
<td>42</td>
<td>Paregoric/phenobarbitone/diazepam</td>
<td>Not stated</td>
<td>Sucking</td>
<td>Average sucking rate 30.5 sucks/min in the paregoric group (n=3), 18.4 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).</td>
</tr>
<tr>
<td>Herzlinger et al[^31]</td>
<td>Diamorphine/methadone</td>
<td>65</td>
<td>Paregoric/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&lt;0.01).</td>
</tr>
<tr>
<td>Kendall et al[^34]</td>
<td>Diamorphine/methadone</td>
<td>132</td>
<td>Tincture of opium/diazepam</td>
<td>Not stated</td>
<td>Seizures</td>
<td>More convulsions seen in infants treated with diazepam (p&lt;0.01).</td>
</tr>
<tr>
<td>Kendall et al[^35]</td>
<td>Methadone</td>
<td>111</td>
<td>Paregoric/phenobarbitone</td>
<td>Randomisation method not stated</td>
<td>Symptom control</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>Pacifco et al[^36]</td>
<td>Diamorphine</td>
<td>25</td>
<td>Morphine/phenobarbitone/diazepam</td>
<td>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>Kahn et al[^37]</td>
<td>Diamorphine</td>
<td>38</td>
<td>Phenoobarbitone/chlorpromazine</td>
<td>Randomisation method not stated</td>
<td>Symptom control</td>
<td>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.</td>
</tr>
<tr>
<td>Finnegan et al[^38]</td>
<td>Opiate/polydrug</td>
<td>139</td>
<td>Paregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Symptom control</td>
<td>Diazepam 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, 24 of 61 phenobarbitone treated and 6 of 9 diazepam treated infants.</td>
</tr>
<tr>
<td>Finnegan and Ehrlich[^39]</td>
<td>Opiate/polydrug</td>
<td>300</td>
<td>Paregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Days to symptom control</td>
<td>Diazepam 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[^40]</td>
<td>Methadone</td>
<td>69</td>
<td>Paregoric/phenobarbitone/diazepam</td>
<td>Randomisation method not stated</td>
<td>Symptom control</td>
<td>Diazepam treated infants, 4.7 in the diazepam treated and 7 in the paregoric treated infants.</td>
</tr>
<tr>
<td>Madden et al[^41]</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[^42]</td>
<td>Methadone</td>
<td>31</td>
<td>Paregoric/phenobarbitone</td>
<td>Randomisation method not stated</td>
<td>Duration of treatment</td>
<td>Mean duration of treatment: 22 days in paregoric treated infants, 17 days in phenobarbitone treated infants (p&lt;0.01).</td>
</tr>
</tbody>
</table>
index, as a consequence it has been recommended that levels should be measured during treatment. Infants may be excessively sleepy and feed poorly. Other potential disadvantages of phenobarbital 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”\[11\]

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**


