The Diagnosis and Treatment of Neonatal Abstinence Syndrome: Clinical Effectiveness and Guidelines
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Acknowledgments:

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.
Research Questions

1. What is the clinical effectiveness of interventions for the diagnosis of neonatal abstinence syndrome?

2. What is the clinical effectiveness of interventions for the treatment of neonatal abstinence syndrome?

3. What are the evidence-based guidelines regarding the diagnosis and treatment of neonatal abstinence syndrome?

Key Findings

Eight systematic reviews, eight randomized controlled trials, and 25 non-randomized studies were identified regarding the diagnosis and treatment of neonatal abstinence syndrome. Additionally, four evidence based guidelines were identified regarding the diagnosis and treatment of neonatal abstinence syndrome.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and April 12, 2017. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Q1-3: Neonates with neonatal abstinence syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q2-3: Women of childbearing age at risk of substance abuse during pregnancy</td>
</tr>
<tr>
<td>Intervention</td>
<td>Q1: Interventions and assessment tools</td>
</tr>
<tr>
<td></td>
<td>Q2: Treatments, either pharmacological or non-pharmacological</td>
</tr>
<tr>
<td></td>
<td>Q3: Guidelines to screen and treat neonatal abstinence syndrome</td>
</tr>
<tr>
<td>Comparator</td>
<td>Q1-2: Any comparator</td>
</tr>
<tr>
<td></td>
<td>Q3: No comparator</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Q1-2: Clinical effectiveness, safety</td>
</tr>
<tr>
<td></td>
<td>Q3: Guidelines</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines</td>
</tr>
</tbody>
</table>
Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Eight systematic reviews, eight randomized controlled trials, and 25 non-randomized studies were identified regarding the diagnosis and/or treatment of neonatal abstinence syndrome. However, due to the volume of identified references, only higher quality evidence [SRs, RCTs] are presented in the main body of the report, with non-randomized studies presented in the appendix. Additionally, four evidence-based guidelines were identified regarding the diagnosis and treatment of neonatal abstinence syndrome. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Eight systematic reviews and eight randomized controlled trials were identified regarding the diagnosis and treatment of neonatal abstinence syndrome (NAS). The eight systematic reviews covered a variety of interventions for NAS including, non-pharmacological treatments (including breastfeeding, swaddling, and acupuncture) and pharmacological treatments (including clonidine, naloxone, and opiates). All eight randomized controlled trials examined pharmacological interventions (including clonidine, methadone, buprenorphine, morphine, etc.) for NAS. These studies are summarized in Table 2.

Four evidence-based guidelines were identified regarding the diagnosis and treatment of NAS. One guideline by Queensland Health provides detailed flow charts regarding the management of NAS, a morphine dosing and weaning schedule, and a phenobarbitone dosing and weaning schedule. This guideline also provides a comprehensive list on diagnosing NAS; their list includes suspecting NAS in any baby who is unsettled, is irritable, has a high pitched cry, has tremors or jitteriness, and/or does not feed well and/or has diarrhea. Another guideline by the Ontario Provincial Council for Maternal and Child Health provides clinical practice recommendations on treatment and diagnosis. The treatment recommendations state that the standard of care in the management of opioid use disorders in women during pregnancy should be methadone, and buprenorphine maintenance treatment should be considered only as an alternative to methadone. Additionally, this guideline recommends that a standardized NAS scoring tool should be used to assess suspected or known cases of in utero opioid exposure. Another guideline by the World Health Organization provides recommendations regarding the identification and management of substance use disorders in pregnancy, including NAS. These recommendations state that evidence of a dose-response relationship between opioid maintenance treatment and NAS has been consistent, which implies all infants should be assessed and, in addition, an opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required. Another guideline aimed to establish clinical practice guidelines for NAS in Ontario; these recommendations include optimizing and standardizing treatment strategies, assessing and managing social risk, increase monitoring of prescribing practices, and facilitating the implementation of better treatment and prevention strategies as they become available.
### Table 2: Summary of Included Studies on Treatment and Diagnosis for Neonatal Abstinence Syndrome

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Reviews</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boucher, 2017¹</td>
<td>8 included studies</td>
<td>Rooming-in care</td>
<td>None</td>
<td>Magnitude of postnatal opioid exposure</td>
<td>Rooming-in care may have decreased postnatal opioid exposure and length of stay in NAS affected infants</td>
</tr>
<tr>
<td></td>
<td>N = NR</td>
<td>Acupuncture</td>
<td></td>
<td>Length of stay</td>
<td>Acupuncture was safe in NAS patients, but its effect on narcotic use and length of stay was inconclusive</td>
</tr>
<tr>
<td>MacMullen, 2016²</td>
<td>24 included studies</td>
<td>Swaddling</td>
<td>Various comparators</td>
<td>Assessment of NAS</td>
<td>An accurate maternal history to determine if the neonate will be at risk should be performed</td>
</tr>
<tr>
<td></td>
<td>N = NR</td>
<td>Breastfeeding</td>
<td>No comparator</td>
<td>Nonpharmacological treatment</td>
<td>Screen all infants at risk with a reliable tool</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cuddling</td>
<td></td>
<td>Pharmacological treatment</td>
<td>Provide supportive measures (i.e., swaddling)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rooming-in</td>
<td></td>
<td></td>
<td>Encourage the maternal-neonatal relationship</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutritional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streetz, 2016³</td>
<td>8 included studies</td>
<td>Clonidine</td>
<td>No comparator</td>
<td>Effectiveness (including treatment time)</td>
<td>Clonidine may be effective, either alone or with other agents</td>
</tr>
<tr>
<td></td>
<td>N = NR</td>
<td>Other agents</td>
<td></td>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Bagley, 2014⁴</td>
<td>4 included studies</td>
<td>Assessment of NAS</td>
<td>Various comparator</td>
<td>Assessment of NAS</td>
<td>Nonpharmacological interventions, especially breastfeeding, may decrease NAS severity</td>
</tr>
<tr>
<td></td>
<td>N = NR</td>
<td>Nonpharmacological treatment</td>
<td>No comparator</td>
<td>Nonpharmacological treatment</td>
<td>Opioid medications such as morphine or methadone were recommended as first-line therapy; phenobarbital or clonidine as second-line adjunctive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharmacological treatment</td>
<td></td>
<td>Pharmacological treatment</td>
<td></td>
</tr>
<tr>
<td>Thirimon, 2013³</td>
<td>9 included</td>
<td>Naloxone</td>
<td>No drug</td>
<td>Respiratory</td>
<td>Evidence is</td>
</tr>
</tbody>
</table>

[¹, ², ³, ⁴] Numbers correspond to footnotes.
### Table 2: Summary of Included Studies on Treatment and Diagnosis for Neonatal Abstinence Syndrome

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Osborn, 2010⁶      | • 7 included studies  
• N = 385          | • Sedative       | • Non-opiate control | • Effectiveness  
• Safety          | • Infants with NAS suffering from opiate withdrawal should be initially treated with an opiate  
• Additionally to being treated with an opiate, phenobarbitone or clonidine may reduce withdrawal severity  
• When a sedative is used, phenobarbitone should be used in preference to diazepam |
| Osborn, 2010⁷      | • 9 included studies  
• N = 645          | • Opiate         | • Non-pharmacological treatment | • Effectiveness  
• Safety          | • When comparing opiates to supportive care, opiates may reduce time to regain birth weight, but increase duration of hospital stay  
• Opiates may reduce the incidence of seizures when compared to phenobarbitone  
• Opiates reduced the incidence of treatment failure when compared to diazepam |
| Van Sleuwen, 2007⁸ | • Number of included studies NR  
• N = NR          | • Swaddling      | • NR            | • Effectiveness  
• Safety          | • Swaddling is supportive in cases of NAS |
| Bada, 2015⁹       | • N = 31            | • Morphine      | • Clonidine    | • Neurobehavioural performance | • Clonidine may be a favourable alternative to morphine to treat infants with NAS |
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</tr>
</thead>
<tbody>
<tr>
<td>Brown, 2015&lt;sup&gt;10&lt;/sup&gt;</td>
<td>• N = 78</td>
<td>• Methadone</td>
<td>• Morphine</td>
<td>• Duration of treatment for NAS</td>
<td>• Methadone had a shorter treatment length of than morphine</td>
</tr>
<tr>
<td>Nayeri, 2015&lt;sup&gt;11&lt;/sup&gt;</td>
<td>• N = 60</td>
<td>• Oral morphine sulfate</td>
<td>• Phenobarbital</td>
<td>• Duration of treatment</td>
<td>• Duration of hospital stay</td>
</tr>
<tr>
<td>Raith, 2015&lt;sup&gt;12&lt;/sup&gt;</td>
<td>• N = 28</td>
<td>• Acupuncture with pharmacological treatment</td>
<td>• Pharmacological treatment alone</td>
<td>• Duration of treatment</td>
<td>• Acupuncture with pharmacological treatment significantly reduced the duration of morphine treatment in newborns with NAS</td>
</tr>
<tr>
<td>Surran, 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>• N = 68</td>
<td>• Clonidine</td>
<td>• Phenobarbital</td>
<td>• Duration of treatment</td>
<td>• Phenobarbital had significantly longer therapy time when compared with clonidine in infants with NAS</td>
</tr>
<tr>
<td>Kraft, 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>• N = 24</td>
<td>• Sublingual buprenorphine</td>
<td>• Morphine</td>
<td>• Safety</td>
<td>• Duration of treatment</td>
</tr>
<tr>
<td>Agthe, 2009&lt;sup&gt;15&lt;/sup&gt;</td>
<td>• N = 80</td>
<td>• Clonidine</td>
<td>• Placebo</td>
<td>• Duration of therapy</td>
<td>• Safety</td>
</tr>
<tr>
<td>Kraft, 2008&lt;sup&gt;16&lt;/sup&gt;</td>
<td>• N = 13</td>
<td>• Sublingual buprenorphine</td>
<td>• Neonatal opium solution</td>
<td>• Safety</td>
<td>• Duration of treatment</td>
</tr>
</tbody>
</table>

Abbreviations: NAS = neonatal abstinence syndrome; NR = not reported.
References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses


Randomized Controlled Trials


Guidelines and Recommendations


PubMed: PM23241498
Appendix — Further Information

Previous CADTH Reports


Non-Randomized Studies


Clinical Practice Guideline – Uncertain Methodology