

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

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

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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

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

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 reviews¹⁻⁸ and eight randomized controlled trials⁹⁻¹⁶ 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 treatment^{1-2,4,8} (including breastfeeding, swaddling, and acupuncture) and pharmacological treatments²⁻⁷ (including clonidine, naloxone, and opiates). All eight randomized controlled trials⁹⁻¹⁶ examined pharmacological interventions (including clonidine, methadone, buprenorphine, morphine, etc.) for NAS. These studies are summarized in Table 2.

Four evidence-based guidelines¹⁷⁻²⁰ were identified regarding the diagnosis and treatment of NAS. One guideline¹⁷ 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 guideline¹⁷ 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 guideline¹⁸ 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 guideline¹⁸ recommends that a standardized NAS scoring tool should be used to assess suspected or known cases of in utero opioid exposure. Another guideline¹⁹ 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 guideline²⁰ 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

First Author, Year	Study Characteristics	Intervention(s)	Comparator(s)	Outcomes	Conclusions
Systematic Reviews					
Boucher, 2017¹	<ul style="list-style-type: none"> • 8 included studies • N = NR 	<ul style="list-style-type: none"> • Rooming-in care • Acupuncture 	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Magnitude of postnatal opioid exposure • Length of stay 	<ul style="list-style-type: none"> • Rooming-in care may have decreased postnatal opioid exposure and length of stay in NAS affected infants • Acupuncture was safe in NAS patients, but its effect on narcotic use and length of stay was inconclusive
MacMullen, 2016²	<ul style="list-style-type: none"> • 24 included studies • N = NR 	<ul style="list-style-type: none"> • Swaddling • Breastfeeding • Cuddling • Rooming-in • Nutritional Support • Various forms of room therapy • Pharmacological treatment 	<ul style="list-style-type: none"> • Various comparators • No comparator 	<ul style="list-style-type: none"> • Assessment of NAS • Nonpharmacological treatment • Pharmacological treatment 	<ul style="list-style-type: none"> • An accurate maternal history to determine if the neonate will be at risk should be performed • Screen all infants at risk with a reliable tool • Provide supportive measures (i.e., swaddling) • Encourage the maternal-neonatal relationship
Streetz, 2016³	<ul style="list-style-type: none"> • 8 included studies • N = NR 	<ul style="list-style-type: none"> • Clonidine 	<ul style="list-style-type: none"> • No comparator • Other agents 	<ul style="list-style-type: none"> • Effectiveness (including treatment time) • Safety 	<ul style="list-style-type: none"> • Clonidine may be effective, either alone or with other agents
Bagley, 2014⁴	<ul style="list-style-type: none"> • 4 included studies • N = NR 	<ul style="list-style-type: none"> • Assessment of NAS • Nonpharmacological treatment • Pharmacological treatment 	<ul style="list-style-type: none"> • Various comparator • No comparator 	<ul style="list-style-type: none"> • Assessment of NAS • Nonpharmacological treatment • Pharmacological treatment 	<ul style="list-style-type: none"> • Nonpharmacological interventions, especially breastfeeding, may decrease NAS severity • Opioid medications such as morphine or methadone were recommended as first-line therapy; phenobarbital or clonidine as second-line adjunctive therapy
Thirimon, 2013⁵	<ul style="list-style-type: none"> • 9 included 	<ul style="list-style-type: none"> • Naloxone 	<ul style="list-style-type: none"> • No drug 	<ul style="list-style-type: none"> • Respiratory 	<ul style="list-style-type: none"> • Evidence is

Table 2: Summary of Included Studies on Treatment and Diagnosis for Neonatal Abstinence Syndrome

First Author, Year	Study Characteristics	Intervention(s)	Comparator(s)	Outcomes	Conclusions
	<ul style="list-style-type: none"> studies N = NR 		<ul style="list-style-type: none"> Placebo 	function	insufficient to determine the efficacy of naloxone
Osborn, 2010⁵	<ul style="list-style-type: none"> 7 included studies N = 385 	<ul style="list-style-type: none"> Sedative 	<ul style="list-style-type: none"> Non-opiate control 	<ul style="list-style-type: none"> Effectiveness Safety 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 9 included studies N = 645 	<ul style="list-style-type: none"> Opiate 	<ul style="list-style-type: none"> Sedative Non-pharmacological treatment 	<ul style="list-style-type: none"> Effectiveness Safety 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Number of included studies NR N = NR 	<ul style="list-style-type: none"> Swaddling 	<ul style="list-style-type: none"> NR 	<ul style="list-style-type: none"> Effectiveness Safety 	<ul style="list-style-type: none"> Swaddling is supportive in cases of NAS
Randomized Controlled Trials					
Bada, 2015⁹	<ul style="list-style-type: none"> N = 31 	<ul style="list-style-type: none"> Morphine 	<ul style="list-style-type: none"> Clonidine 	<ul style="list-style-type: none"> Neurobehavioural performance 	<ul style="list-style-type: none"> Clonidine may be a favourable alternative to morphine to treat infants with NAS

Table 2: Summary of Included Studies on Treatment and Diagnosis for Neonatal Abstinence Syndrome

First Author, Year	Study Characteristics	Intervention(s)	Comparator(s)	Outcomes	Conclusions
Brown, 2015¹⁰	<ul style="list-style-type: none"> N = 78 	<ul style="list-style-type: none"> Methadone 	<ul style="list-style-type: none"> Morphine 	<ul style="list-style-type: none"> Duration of treatment for NAS 	<ul style="list-style-type: none"> Methadone had a shorter treatment length of than morphine
Nayeri, 2015¹¹	<ul style="list-style-type: none"> N = 60 	<ul style="list-style-type: none"> Oral morphine sulfate 	<ul style="list-style-type: none"> Phenobarbital 	<ul style="list-style-type: none"> Duration of treatment Duration of hospital stay Requirement of adjunctive treatment 	<ul style="list-style-type: none"> There were no significant differences between the two treatments
Raith, 2015¹²	<ul style="list-style-type: none"> N = 28 	<ul style="list-style-type: none"> Acupuncture with pharmacological treatment 	<ul style="list-style-type: none"> Pharmacological treatment alone 	<ul style="list-style-type: none"> Duration of treatment 	<ul style="list-style-type: none"> Acupuncture with pharmacological treatment significantly reduced the duration of morphine treatment in newborns with NAS
Surran, 2013¹³	<ul style="list-style-type: none"> N = 68 	<ul style="list-style-type: none"> Clonidine 	<ul style="list-style-type: none"> Phenobarbital 	<ul style="list-style-type: none"> Duration of treatment 	<ul style="list-style-type: none"> Phenobarbital had significantly longer therapy time when compared with clonidine in infants with NAS
Kraft, 2011¹⁴	<ul style="list-style-type: none"> N = 24 	<ul style="list-style-type: none"> Sublingual buprenorphine 	<ul style="list-style-type: none"> Morphine 	<ul style="list-style-type: none"> Safety Duration of treatment Duration of hospital stay 	<ul style="list-style-type: none"> Sublingual buprenorphine was safe and more effective over morphine in infants with NAS
Agthe, 2009¹⁵	<ul style="list-style-type: none"> N = 80 	<ul style="list-style-type: none"> Clonidine 	<ul style="list-style-type: none"> Placebo 	<ul style="list-style-type: none"> Duration of therapy Safety Effectiveness 	<ul style="list-style-type: none"> Clonidine reduced the duration of pharmacotherapy for NAS without causing short-term adverse cardiovascular outcomes
Kraft, 2008¹⁶	<ul style="list-style-type: none"> N = 13 	<ul style="list-style-type: none"> Sublingual buprenorphine 	<ul style="list-style-type: none"> Neonatal opium solution 	<ul style="list-style-type: none"> Safety Duration of treatment 	<ul style="list-style-type: none"> Sublingual buprenorphine was safe and may be a novel treatment to treat NAS

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

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Boucher AM. Nonopioid management of neonatal abstinence syndrome. *Adv Neonatal Care*. 2017 Apr;17(2):84-90.
[PubMed: PM28002062](#)
2. MacMullen NJ, Dulski LA, Blobaum P. Evidence-based interventions for neonatal abstinence syndrome. *Peds Nurs*. 2014 Jul-Aug;40(4):165-72, 203. Available from: <https://www.pediatricnursing.net/ce/2016/article40051.pdf>
[PubMed: PM: 25269356](#)
3. Streetz VN, Gildon BL, Thompson DF. Role of clonidine in neonatal abstinence syndrome: a systematic review. *Ann Pharmacother*. 2016 Apr;50(4):301-10.
[PubMed: PM26783353](#)
4. Bagley SM, Wachman EM, Holland E, Brogly SB. Review of the assessment and management of neonatal abstinence syndrome. *Addict Sci Clin Pract*. 2014 Sep 9;9(1):19. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4166410>
[PubMed: PM25199822](#)
5. Moe-Byrne T, Brown JVE, McGuire W. Naloxone for opiate-exposed newborn infants. *Cochrane Database Sys Rev*. 2013 Feb 28;(2):CD003483. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003483.pub2/abstract>
[PubMed: PM 23450541](#)
6. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev*. 2010 Oct 6;(10):CD002053.
[PubMed: PM20927729](#)
7. Osborn DA, Jeffery HE, Cole MJ. Opiate treatment for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev*. 2010 Oct 6;(10):CD002059.
[PubMed: PM20927730](#)
8. Van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpden TW, L'Hoir MP. Swaddling: a systematic review. *Pediatrics*. 2007 Oct;120(4):e1097-e1106.
[PubMed: PM17908730](#)

Randomized Controlled Trials

9. Bada HS, Sithisarn T, Gibson J, Garlitz K, Caldwell R, Capilouto G, et al. Morphine versus clonidine for neonatal abstinence syndrome. *Pediatrics*. 2015 Feb;135(2):e383-e391.
[PubMed: PM25624389](#)
10. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol*. 2015 Apr;35(4):278-83.
[PubMed: PM25357093](#)

11. Nayeri F, Sheikh M, Kalani M, Niknafs P, Shariat M, Dalili H, et al. Phenobarbital versus morphine in the management of neonatal abstinence syndrome, a randomized control trial. *BMC Pediatr.* 2015 May 15;15:57. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4438473>
[PubMed: PM25976238](#)
12. Raith W, Schmolzer GM, Resch B, Reiterer F, Avian A, Koestenberger M, et al. Laser acupuncture for neonatal abstinence syndrome: a randomized controlled trial. *Pediatrics.* 2015 Nov;136(5):876-84.
[PubMed: PM26504123](#)
13. Surran B, Visintainer P, Chamberlain S, Kopcza K, Shah B, Singh R. Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome. A prospective randomized clinical trial. *J Perinatol.* 2013 Dec;33(12):954-9.
[PubMed: PM23949834](#)
14. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction.* 2011 Mar;106(3):574-80. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3022999>
[PubMed: PM20925688](#)
15. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics.* 2009 May;123(5):e849-e856. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746902>
[PubMed: PM19398463](#)
16. Kraft WK, Gibson E, Dysart K, Damle VS, Larusso JL, Greenspan JS, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. *Pediatrics.* 2008 Sep;122(3):e601-e607. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574639>
[PubMed: PM18694901](#)

Guidelines and Recommendations

17. Queensland Health [Internet]. Perinatal substance abuse: neonatal. Brisbane, Queensland, Australia: Queensland Clinical Guidelines, Queensland Health; 2016 [cited 2017 Apr 26]. Available from: https://www.health.qld.gov.au/_data/assets/pdf_file/0018/140814/g-psuneo.pdf
Supplement available: https://www.health.qld.gov.au/_data/assets/pdf_file/0013/141007/s-psuneo.pdf
18. Provincial Council for Maternal and Child Health. Neonatal abstinence syndrome (NAS): clinical practice guidelines [Internet]. Toronto (ON) : Provincial Council for Maternal and Child Health; 2016 [updated]. Available from : <http://www.pcmch.on.ca/wp-content/uploads/2016/12/NAS-Clinical-Guideline-Update-2016Nov25.pdf>
Summary of recommendations available: <http://www.pcmch.on.ca/wp-content/uploads/2016/12/NAS-Clinical-Guideline-Update-Summary-of-Recommendations-2016Nov25.pdf>

19. National Guideline Clearinghouse. Guideline summary: guidelines for the identification and management of substance use and substance use disorders in pregnancy. In: National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2014 [cited 2017 Apr 26]. NGC summary available: <https://www.guideline.gov/summaries/summary/48894/guidelines-for-the-identification-and-management-of-substance-use-and-substance-use-disorders-in-pregnancy?q=neonatal+abstinence>
20. Dow K, Ordean A, Murphy-Oikonen J, Pereira J, Koren G, Roukema H, et al. Neonatal abstinence syndrome clinical practice guidelines for Ontario. J Popul Ther Clin Pharmacol. 2012;19(3):e488-e506. Available from: <http://www.jptcp.com/articles/neonatal-abstinence-syndrome-clinical-practice-guidelines-for-ontario.pdf>
[PubMed: PM23241498](#)

Appendix — Further Information

Previous CADTH Reports

21. CADTH. Using Naloxone to treat narcotic-exposed infants: clinical benefits, harms, and guidelines for use [Internet]. Ottawa (ON): CADTH; 2008 [cited 2017 Apr 26]. Available from:
<https://www.cadth.ca/sites/default/files/pdf/htis/J0148%20Naloxone%20to%20Treat%20Narcotic-Exposed%20Infants%20final.pdf>

Non-Randomized Studies

22. Howard MB, Schiff DM, Penwill N, Si W, Rai A, Wolfgang T, et al. Impact of parental presence at infants' bedside on neonatal abstinence syndrome. *Hosp Pediatr*. 2017 Feb;7(2):63-9.
[PubMed: PM28137920](#)
23. Mucke S, Nagel M, Siedentopf J, Buhner C, Huseman D. Neonatal abstinence syndrome: twelve years of experience at a regional referral center. *Klin Padiatr*. 2017 Jan;229(1):32-9.
[PubMed: PM27723910](#)
24. Hall ES, Isemann BT, Wexelblatt SL, Meinzen-Derr J, Wiles JR, Harvey S, et al. A cohort comparison of buprenorphine versus methadone treatment for neonatal abstinence syndrome. *J Pediatr*. 2016 Mar;170:39-44.
[PubMed: PM26703873](#)
25. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics*. 2016 Jun;137(6).
[PubMed: PM27194629](#)
26. Oji-Mmuo CN, Michael EJ, McLatchy J, Lewis MM, Becker JE, Doheny KK. Skin conductance at baseline and postheel lance reflects sympathetic activation in neonatal opiate withdrawal. *Acta Paediatr*. 2016 Mar;105(3):e99-e106. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4747688>
[PubMed: PM26613197](#)
27. Hall ES, Meinzen-Derr J, Wexelblatt SL. Cohort analysis of a pharmacokinetic-modeled methadone weaning optimization for neonatal abstinence syndrome. *J Pediatr*. 2015 Dec;167(6):1221-5.
[PubMed: PM26477866](#)
28. Kelly LE, Knoppert D, Roukema H, Rieder MJ, Koren G. Oral morphine weaning for neonatal abstinence syndrome at home compared with in-hospital: an observational cohort study. *Paediatr Drugs*. 2015 Apr;17(2):151-7.
[PubMed: PM25342143](#)
29. Newman A, Davies GA, Dow K, Holmes B, Macdonald J, McKnight S, et al. Rooming-in care for infants of opioid-dependent mothers: implementation and evaluation at a tertiary care hospital. *Can Fam Physician*. 2015 Dec;61(12):e555-e561. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677958>
[PubMed: PM27035006](#)

30. Young ME, Hager SJ, Spurlock D, Jr. Retrospective chart review comparing morphine and methadone in neonates treated for neonatal abstinence syndrome. *Am J Health Syst Pharm*. 2015 Dec 1;72(23 Suppl 3):S162-S167.
[PubMed: PM26582303](#)
31. Hall ES, Wexelblatt SL, Crowley M, Grow JL, Jasin LR, Klebanoff MA, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*. 2014 Aug;134(2):e527-e534. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4531273>
[PubMed: PM25070317](#)
32. Johnson MR, Nash DR, Laird MR, Kiley RC, Martinez MA. Development and implementation of a pharmacist-managed, neonatal and pediatric, opioid-weaning protocol. *J Pediatr Pharmacol Ther*. 2014 Jul;19(3):165-73. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4187529>
[PubMed: PM25309146](#)
33. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004-2011. *J Perinatol*. 2014 Nov;34(11):867-72.
[PubMed: PM24921412](#)
34. Smirk CL, Bowman E, Doyle LW, Kamlin CO. How long should infants at risk of drug withdrawal be monitored after birth? *J Paediatr Child Health*. 2014 May;50(5):352-5.
[PubMed: PM24628977](#)
35. Smirk CL, Bowman E, Doyle LW, Kamlin O. Home-based detoxification for neonatal abstinence syndrome reduces length of hospital admission without prolonging treatment. *Acta Paediatr*. 2014 Jun;103(6):601-4.
[PubMed: PM24547949](#)
36. Hunseler C, Bruckle M, Roth B, Kribs A. Neonatal opiate withdrawal and rooming-in: a retrospective analysis of a single center experience. *Klin Padiatr*. 2013 Sep;225(5):247-51.
[PubMed: PM23966227](#)
37. Kokotajlo S, Robinson CA, Presti A. Use of tincture of opium compared to oral morphine for the treatment of neonatal abstinence syndrome. *J Opioid Manag*. 2013 Jan;9(1):62-70.
[PubMed: PM23709305](#)
38. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *Acta Paediatr*. 2013 Nov;102(11):1060-6.
[PubMed: PM23909865](#)
39. Backes CH, Backes CR, Gardner D, Nankervis CA, Giannone PJ, Cordero L. Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting. *J Perinatol*. 2012 Jun;32(6):425-30. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3682112>
[PubMed: PM21852772](#)

40. Gordon AL, Lopatko OV, Haslam RR, Stacey H, Pearson V, Woods A, et al. Ineffective morphine treatment regimen for the control of neonatal abstinence syndrome in buprenorphine- and methadone-exposed infants. *J Dev Orig Health Dis.* 2012 Aug;3(4):262-70.
[PubMed: PM25102147](#)
41. Abrahams RR, Kay-Dunn MH, Nevmerjitskaia V, MacRae GS, Payne SP, Hodgson ZG. An evaluation of rooming-in among substance-exposed newborns in British Columbia. *J Obstet Gynaecol Can.* 2010 Sep;32(9):866-71.
[PubMed: PM21050520](#)
42. Esmaili A, Keinhorst AK, Schuster T, Beske F, Schlosser R, Bastanier C. Treatment of neonatal abstinence syndrome with clonidine and chloral hydrate. *Acta Paediatr.* 2010 Feb;99(2):209-14.
[PubMed: PM19839963](#)
43. Jones HE, Harrow C, O'Grady KE, Crocetti M, Jansson LM, Kaltenbach K. Neonatal abstinence scores in opioid-exposed and nonexposed neonates: a blinded comparison. *J Opioid Manag.* 2010 Nov;6(6):409-13.
[PubMed: PM21269001](#)
44. Murphy-Oikonen J, Montelpare WJ, Southon S, Bertoldo L, Persichino N. Identifying infants at risk for neonatal abstinence syndrome: a retrospective cohort comparison study of 3 screening approaches. *J Perinat Neonatal Nurs.* 2010 Oct;24(4):366-72.
[PubMed: PM21045617](#)
45. Saiki T, Lee S, Hannam S, Greenough A. Neonatal abstinence syndrome--postnatal ward versus neonatal unit management. *Eur J Pediatr.* 2010 Jan;169(1):95-8.
[PubMed: PM19440732](#)
46. Abrahams RR, Kelly SA, Payne S, Thiessen PN, Mackintosh J, Janssen PA. Rooming-in compared with standard care for newborns of mothers using methadone or heroin. *Can Fam Physician.* 2007 Oct;53(10):1722-30. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2231437>
[PubMed: PM17934036](#)
47. Ebner N, Rohrmeister K, Winklbaaur B, Baewert A, Jagsch R, Peternell A, et al. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend.* 2007 Mar 16;87(2-3):131-8.
[PubMed: PM17000060](#)

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48. Casper T, Arbour M. Evidence-based nurse-driven interventions for the care of newborns with neonatal abstinence syndrome. *Adv Neonatal Care.* 2014 Dec;14(6):376-80.
[PubMed: PM25068529](#)