JAMA | Review

Neonatal Abstinence Syndrome
Advances in Diagnosis and Treatment

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IMPORTANCE Neonatal abstinence syndrome, which occurs as a result of in utero opioid exposure, affects between 6.0 and 20 newborns per 1000 live US births. There is substantial variability in how neonatal abstinence syndrome is diagnosed and managed.

OBJECTIVE To summarize key studies examining the diagnosis and management (both pharmacologic and nonpharmacologic) of neonatal abstinence syndrome published during the past 10 years.

EVIDENCE REVIEW PubMed, Web of Science, and CINAHL were searched for articles published between July 1, 2007, and December 31, 2017. Abstracts were screened and included in the review if they pertained to neonatal abstinence syndrome diagnosis or management and were judged by the authors to be clinical trials, cohort studies, or case series.

FINDINGS A total of 53 articles were included in the review, including 9 randomized clinical trials, 35 cohort studies, 1 cross-sectional study, and 8 case series—representing a total of 11 905 unique opioid-exposed mother-infant dyads. Thirteen studies were identified that evaluated established or novel neonatal abstinence syndrome assessment methods, such as brief neonatal abstinence syndrome assessment scales or novel objective physiologic measures to predict withdrawal. None of the new techniques that measure infant physiologic parameters are routinely used in clinical practice. The most substantial number of studies of neonatal abstinence syndrome management pertain to nonpharmacologic care—specifically, interventions that promote breastfeeding or encourage parents to room-in with their newborns. Although these nonpharmacologic interventions appear to decrease the need for pharmacologic treatment and result in shorter hospitalizations, the interventions are heterogeneous and there are no high-quality clinical trials to support them. Regarding pharmacologic interventions, only 5 randomized clinical trials with prespecified sample size calculations (4 infant, 1 maternal treatment) have been published. Each of these trials was small (from 26 to 131 participants) and tested different therapies, limiting the extent to which results can be aggregated. There is insufficient evidence to support an association between any diagnostic or treatment approach and differential neurodevelopmental outcomes among infants with neonatal abstinence syndrome.

CONCLUSIONS AND RELEVANCE Evidence pertaining to the optimal diagnosis and treatment strategies for neonatal abstinence syndrome is based on small or low-quality studies that focus on intermediate outcomes, such as need for pharmacologic treatment or length of hospital stay. Clinical trials are needed to evaluate health and neurodevelopmental outcomes associated with objective diagnostic approaches as well as pharmacologic and nonpharmacologic treatment modalities.

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Neonatal abstinence syndrome (NAS), also referred to as neonatal opioid withdrawal syndrome, is defined by signs and symptoms of withdrawal that infants develop after in utero exposure to opioids.[1,2] Newborns typically experience signs of withdrawal 2 to 3 days after birth, and infants whose symptoms are severe enough to require pharmacologic intervention are typically treated with replacement opioids such as methadone or morphine, and then weaned off over days to weeks.[2] In 2012, the mean length of hospitalization in the United States for all infants with NAS was 16.0 days (95% CI, 16.0-17.7) and 23.0 days (95% CI, 22.2-23.8) for those requiring pharmacologic treatment, with substantial variability across centers.[3-5]

The incidence of NAS in 2012 was estimated to be 6.0 per 1000 live US births—a 5-fold increase since 2000.[3,4] Since 2012, the incidence has continued to increase, with data in 2016 from 23 hospitals in the US Pediatric Health Information System showing an incidence of 20 per 1000 live births.[6] There is wide variation in the care of opioid-exposed newborns, without current consensus as to the best diagnostic or treatment strategies. There are also increasing concerns from cohort studies comparing opioid-exposed children with unexposed controls that in utero exposure adversely influences neurodevelopmental status among school-aged children.[7-9]

In this review, approaches to the diagnosis and treatment of NAS published during the past 10 years are reviewed, including assessment of NAS by clinicians, new diagnostic tools, and instruments designed to predict infants' subsequent need for pharmacologic treatment. The extent to which strategies for infant nonpharmacologic and pharmacologic treatment—as well as maternal pharmacologic treatment—have affected intermediate and health outcomes for infants with NAS is also reviewed. Current knowledge about the association of diagnostic or treatment approaches with infants' neurodevelopmental outcomes is summarized. Key gaps in evidence are outlined.

Key Points

Question What are the recent advances in the diagnosis and treatment of neonatal abstinence syndrome?

Findings Novel methods are being developed to assess and diagnose neonatal abstinence syndrome objectively, but none are routinely used in clinical practice. Nonpharmacologic interventions may decrease the need for pharmacologic treatment; however, there are no high-quality randomized clinical trials to support these nonpharmacologic interventions, and there are few randomized studies with prespecified sample size calculations to support pharmacologic treatment regimens. Data concerning neurodevelopmental outcomes are limited.

Meaning Nonpharmacologic interventions represent the most substantial changes in the treatment of neonatal abstinence syndrome. High-quality randomized studies are necessary to demonstrate the effectiveness of new diagnostic approaches and pharmacologic and nonpharmacologic interventions.

Methods

We reviewed PubMed, Web of Science, and CINAHL electronic databases for peer-reviewed studies published between July 1, 2007, and December 31, 2017. Search terms included *neonatal abstinence syndrome, substance-exposed newborn, neonatal drug withdrawal, opioid dependency, pregnancy, perinatal substance use, treatment*, and *outcomes*, among others (eFigure 1 in the Supplement). The search was limited to English-language studies and included clinical trials, cohort studies, and case series. Commentaries, opinion pieces, epidemiologic studies, review articles, meta-analyses, and case studies were excluded. In addition to searching the current published literature, we reviewed ClinicalTrials.gov for ongoing trials related to NAS (eTable 1 in the Supplement).

The studies were categorized into 4 groups based on their evaluation of NAS assessment and diagnosis, infant nonpharmacologic treatment, infant pharmacologic treatment, and maternal pharmacologic treatment. Regarding assessment and diagnosis, we included studies that compared novel assessment methods with existing tools (the Finnegan scale)[10] and studies that reported the extent to which novel assessment methods or new scoring algorithms of existing scales predicted, or affected, infant pharmacologic treatment rates. Studies were defined as infant nonpharmacologic treatment if they evaluated factors concerning the location of care, supportive care, and type of weaning protocol used to guide infant pharmacologic management. Studies were defined as pharmacologic treatment if they compared 2 or more medication regimens. Maternal and infant treatment studies were included if they evaluated either short-term NAS outcomes (Finnegan scores, need for pharmacologic treatment, total opioid treatment days, or length of hospital stay) or neurodevelopmental outcomes (as assessed with a standardized neurodevelopmental scale). Because the focus of this review was to evaluate the association between NAS assessment or treatment modalities and infant outcomes, studies on neurodevelopmental outcomes were included only if they compared outcomes across 2 or more treatment modalities.

Within each category, if high-quality studies existed, as defined by the existence of both randomized clinical trials (RCTs) with prespecified sample size calculations and corroborating meta-analyses, lower-quality studies were not reviewed individually. An exception was made for cohort studies that specifically assessed neurodevelopmental outcomes, since such studies are uncommon and particularly salient to the field. Thus, for maternal treatment studies (the only main category to which this rule applied) that reported NAS hospitalization outcomes only, the scope was limited to clinical trials. However, for maternal treatment studies that examined infant neurodevelopmental outcomes, cohort studies were included as well.

Two reviewers (E.M.W. and D.M.S.) reviewed abstracts, met to review the full text of articles, and determined studies that met inclusion criteria for the review. Reference lists for 3 recently published systematic reviews were evaluated to ensure that no relevant articles had been excluded (these reviews focused on the clinical presentation and epidemiology of NAS and the treatment of pregnant women with opioid use disorders).[11-13] Articles were graded using the quality rating scheme adapted from the Oxford Centre for Evidence-based Medicine's level of evidence and grades of

recommendations.[14] Because of the relatively small sample sizes of the included randomized trials and concerns about the misinterpretation of pilot study data,[15] the highest level (grade "1") rating was given to randomized trials only if authors provided prespecified sample size calculations.[15]

Each study was reviewed by 2 investigators; if they disagreed on an evidence rating, a third investigator (M.S.) reviewed the study and all reviewers discussed the study design and grade until consensus was reached. Seventeen articles required review by all investigators. Discrepancies were most common around designating a study a case series vs retrospective cohort. In this case, the framework established by Dekkers and colleagues was used to guide the assessment.[16]

Results

Search Results

The search yielded 1177 unique results. Ninety full-text articles met the inclusion criteria based on the abstracts and were reviewed; 53 original research articles were included in the final review (eFigure 1 in the Supplement). We evaluated 9 RCTs (of which 4 infant treatment studies and 1 maternal treatment study provided prespecified sample size calculations), 35 cohort studies, 8 case series, and 1 cross-sectional study—which included a total of 11 905 unique opioid-exposed mother-infant dyads. Thirteen original research reports on infant diagnosis and assessment, 25 on infant nonpharmacologic treatment, 11 on infant pharmacologic treatment, and 4 on maternal pharmacologic treatment were reviewed.

Studies Examining Diagnosis and Assessment

Comparing Novel Assessment Methods With Existing Tools

One retrospective cohort study (**Table 1**) compared a novel 7-item "short form" with the original Finnegan scale (a 21-item scale, which is the most widely used tool to assess NAS symptoms)[10] and found that the short-form score correlated highly (r = 0.92, P < .001) with total Finnegan scores.[17] Jones et al found that the original Finnegan scale and an alternative scale—the MOTHER NAS scale, developed for use in an RCT and based in part on the Finnegan scale—had poor internal consistency (Cronbach α<0.62) when infants were assessed at time of first score, time of peak score, and time of first medication administration.[19,30] Nagiub et al[18] found that neonatal heart rate measurements on days 1, 2, and 3 of life correlated with Finnegan assessments performed at those same time points (r = 0.235, P = .001).

Comparing Novel Methods With Pharmacologic Treatment Rates

There were 5 cohort studies that examined the association between new NAS assessment scales and the need for pharmacologic treatment. Chisamore et al[22] examined different Finnegan score thresholds for the initiation of treatment and found that 73% of infants met criteria for pharmacologic treatment when a single score of 9 or higher was used, as opposed to 26% when a threshold of 3 scores higher than 8 or 2 scores higher than 11 were used (adjusted odds ratio, 7.0; 95% CI, 3.4-14.5). Jones et al[23] found in a secondary analysis that a 5-item "short form" of the MOTHER NAS scale was able to discriminate infants who proceeded to need pharmacologic treatment from those who did not (area under the curve = 0.87, SE, 0.03; P < .001). In a retrospective cohort study, Isemann et al[26] developed 2 prediction tools from modified Finnegan scores. One was a symptom-based prediction tool (score range 0-5) assessing muscle tone, tremors, and skin excoriations, which had a positive predictive value (PPV) of 100% for pharmacologic treatment using a cut-point score of 4 or higher. A symptom plus exposure tool (taking into account maternal opioid; score range 0-7) had a PPV of 86% for pharmacologic treatment using a cut-point of 5 or higher. Grossman et al,[25] within the context of a multi-intervention quality improvement study, developed a novel approach that in lieu of a numerical score used regular assessments of the infant's ability to eat, sleep, and be consoled to determine need for pharmacologic treatment. Infants assessed with this method, which occurred in combination with other nonpharmacologic interventions, had a 45% reduction (73% vs 28%) in initiation of pharmacologic treatment.[25] Grossman et al also performed a secondary analysis of 50 infants who were assessed with both the Eat, Sleep, Console approach and the Finnegan score; they found that fewer infants met criteria to initiate pharmacologic treatment with the Eat, Sleep, Console approach (12% vs 62%).[29]

There have been 4 prospective cohort studies and 1 case series all with limited sample sizes (range 12-104 participants) that examined the association between novel physiologic tools and pharmacologic treatment rates.[20,21,24,27,28] Jansson et al[20] found that an increase in maternal vagal tone after methadone dosing, as measured by electrocardiogram monitoring at 36 weeks' gestation, was associated with a 2.9-fold (P < .05) increase in rates of infant pharmacologic treatment. Leeman et al[21] found that intrapartum fetal heart rate tracings did not reliably predict the need for pharmacotherapy. Two studies by Oji-Mmuo et al[24,27] found that higher levels of infant skin conductance, representing higher sympathetic tone, was associated with the need for subsequent pharmacologic treatment. Subedi et al[28] measured brain-derived neurotropic factor levels in the first 48 hours after admission to the neonatal intensive care unit (NICU) among infants receiving pharmacologic treatment and found no association with length of hospital stay or number of medications needed to treat NAS. To our knowledge, none of these physiologic assessment modalities are used routinely in clinical practice.[5]

Studies Examining Infant Nonpharmacologic Treatment

Nonpharmacologic interventions that have been studied (**Table 2**) include rooming-in (keeping the mother-infant dyad together for as much of the infant's hospital course as possible; n = 7), breastfeeding or infant feeding (n = 9), acupuncture (n = 1), the location of opioid weans (n = 5), and protocols governing opioid weans (n = 3).

Rooming-In, Breastfeeding, and Infant Feeding Practices

All 7 studies that examined rooming-in were performed retrospectively using preexisting clinical data not collected specifically for the purpose of intervention evaluation. Despite this limitation, these studies demonstrated an association between rooming-in models of care and reduced need for pharmacologic treatment (range, 20%-60% reduction), decrease in total opioid treatment days (mean, 8- to 13-day reduction), shortened length of hospital

Table 1. Studies Examining Diagnostic and Assessment Tools for Neonatal Abstinence Syndrome (NAS)

Source	Location and Years of Study	No. of Centers and Setting	No. of Patients	Study Design	In utero Opioid Exposure	NAS Treatment Protocol	Diagnostic Tool(s)	Primary Outcome	Findings or Conclusions	Grade[a]
Comparison of Novel Methods With Existing Assessment Tools										
Maguire et al,[17] 2013	St Petersburg, Florida, 2010-2012	1 NICU	171	Retrospective cohort	Methadone, other	Morphine	NAS short form (7 item) vs modified Finnegan score	Correlation between total scores	r = 0.92, P < .001	3
Nagiub et al,[18] 2014	Detroit, Michigan, 2011-2012	1 Special care nursery	25 Opioid vs 24 control	Prospective cohort	Methadone, short-acting	Morphine	Heart rate variability	Correlation with Finnegan scores in first 72 h	r = 0.235, P = .001	2
Jones et al,[19] 2016	US and Vienna, Austria, 2016	7 Not specified	131	Retrospective cohort	Methadone, buprenorphine	Morphine	Finnegan scale and MOTHER scale	Internal consistency (Cronbach α)	Both scales with poor internal consistency (α<0.62)	3
Novel Methods and Impact on Infant Pharmacologic Treatment										
Jansson et al,[20] 2007	Baltimore, Maryland, 2002-2004	1 Not specified	50	Prospective cohort	Methadone	Diluted tincture of opium	Maternal vagal tone	Infant pharmacologic intervention	Maternal vagal tone associated with infant medication (F = 3.39), P < .05	2
Leeman et al,[21] 2011	Albuquerque, New Mexico, 2002-2009	1 Nursery and NICU	104	Prospective cohort	Methadone	Methadone	Fetal heart rate	Infant pharmacologic intervention	Fetal heart rate accelerations absent less often in treated infants (1.7% vs 20.8%), P = .007[b]	2
Chisamore et al,[22] 2016	Canada, 2000-2014	1 NICU	146	Retrospective cohort	Methadone, short-acting	Morphine	3 Finnegan scores >8 or 2 scores >11 vs first score ≥9 to initiate treatment	Infant pharmacologic intervention	Higher in the first score ≥9 group (57 [73%] vs 18 [26%]; OR, 7.0; 95% CI, 3.4-14.5)	3
Jones et al,[23] 2016	US and Vienna, Austria, 2016	7 Not specified	131	Retrospective cohort	Methadone, buprenorphine	Morphine	3-5 item short forms of MOTHER scale	Infant pharmacologic intervention prediction AUC	5 item short-form had AUC of 0.87 (SE 0.03), P < .001	3
Oji-Mmuo et al,[24] 2016	Hershey, Pennsylvania, 2012-2014	1 Nursery and NICU	14	Prospective cohort	Methadone, buprenorphine, short-acting	Morphine	Skin conductance	Infant pharmacologic intervention	Higher skin conductance in treated infants (0.12 [SE 0.13] vs 0.04 [SE 0.06], P = .02)[c]	2
Grossman et al,[25] 2017	New Haven, Connecticut, 2008-2016	1 Nursery and pediatric unit	99	Retrospective cohort quality improvement	Methadone	Morphine	Eat, Sleep, Console vs Finnegan	Infant pharmacologic intervention (special process control charts)	28% vs 73%[a]	3
Isemann et al,[26] 2017	Cincinnati, Ohio, 2013-2016	1 NICU	264	Retrospective cohort	Methadone, buprenorphine, other	Methadone, buprenorphine	Symptom only vs symptom + exposure prediction tool	Infant pharmacologic intervention PPV	Symptom only: PPV 100%; symptom + exposure: PPV 86%	3
Oji-Mmuo et al,[27] 2017	Hershey, Pennsylvania, 2017	1 Nursery and NICU	12	Case series	Methadone, buprenorphine, morphine, short-acting	Morphine	Skin conductance	Infant pharmacologic intervention	Higher skin conductance in treated infants (0.51 [SE 0.23] vs 0.11 [SE 0.05], P < .05)[c]	4
Subedi et al,[28] 2017	Kentucky, 2015-2016	1 NICU	34	Prospective cohort	Not specified	Morphine	Brain-derived neurotropic factor levels within 48 h of NICU admission	Mean length of stay, No. of NAS medications	r = 0.07, P = .68; no difference in mean brain-derived neurotropic factor levels in infants treated with 1 vs 2 drugs (MD = 36, 95% CI -64 to 137, P = .47)	2
Grossman et al,[29] 2018	New Haven, Connecticut, 2014-2015	1 Nursery and pediatric unit	50	Retrospective cohort	Methadone, buprenorphine, short-acting	Morphine	Eat, Sleep, Console vs Finnegan	Infant treatment	Lower with Eat, Sleep, Console (6 [12%] vs 31 [62%], P < .001)	3

Abbreviations: AUC, area under the curve; NICU, neonatal intensive care unit; PPV, positive predictive value.

[a] Grading system: 1 = Properly powered and conducted RCT; 2 = well-designed controlled trial without randomization or prospective comparative cohort; 3 = case-control or retrospective cohort; 4 = case series or cross-sectional study; 5 = opinion of respected authorities or case reports.[14]

[b] Number of infants associated with percentages not presented in the manuscript.

[c] Where 95% CIs were not available, we present SE or SD.

Table 2. Studies Examining Nonpharmacologic Care Modalities for the Treatment of Neonatal Abstinence Syndrome (NAS)

Source	Location and Years of Study	No. of Centers and Setting	No. of Patients	Study Design	In utero Opioid Exposure	Infant Treatment	Intervention or Comparison	Primary Outcome	Findings or Conclusions	Grade[a]
Rooming-in and/or Parental Presence										
Abrahams et al,[31] 2007	Canada, 1999-2002	2 Inpatient ward and NICU	106	Retrospective cohort	Methadone, heroin	Morphine	Rooming-in vs historical control + level 2 community hospital	Infant pharmacologic intervention, opioid days (mean)	Adjusted RR, 0.40 (95% CI, 0.20-0.78) vs historical control; 0.39 (95% CI, 0.20-0.75) vs community hospital 5.9 (SD 14.2) vs 18.6 (SD 23.4) historical control; vs 18.6 (SD 20.1) community hospital	3
Abrahams et al,[32] 2010	Canada, 2003-2006	12 Inpatient ward and NICU	952	Retrospective cohort	Not specified	Not specified	Rooming-in vs NICU	Breastfeeding, length of stay (mean)	20.7 (95% CI, 18.6-22.8) vs 10.7 d (95% CI, 9.1-12.3) OR, 2.11 (95% CI, 1.61-2.77)	3
Saiki et al,[33] 2010	United Kingdom, 2002-2007	1 Postnatal ward and NICU	60	Retrospective cohort	Methadone, other	Morphine	Postnatal ward vs NICU	Infant pharmacologic intervention, length of stay (median)	2 (11%) vs 19 (45%), $P = .01$ 15.9 (0-74) vs 12.7 d (3-65), $P = .01$	3
Hünseler et al,[34] 2013	Germany, 2004-2011	1 Neonatal ward	77	Case series	Methadone, buprenorphine, heroin, other	Diluted tincture of opium	Rooming-in vs not	Opioid days (mean)	27 (SD 11.5) vs 35.8 (SD 15.3) d, $P = .043$	4
Newman et al,[35] 2015	Canada, 2012-2013	1 Pediatric ward and NICU	45	Retrospective cohort	Methadone	Morphine	Rooming-in vs NICU	Infant pharmacologic intervention, length of stay (mean)	3 (14.3%) vs 20 (83.3%), $P < .001$ 7.9 (SD 7.8) vs 24.8 d (SD 15.6), $P < .001$	3
Holmes et al,[36] 2016	Hanover, New Hampshire, 2012-2015	1 Pediatric ward and NICU	163	Quality improvement initiative	Methadone, buprenorphine, other	Morphine	Rooming-in, standardized assessments, nonpharmacologic care	Infant pharmacologic intervention, length of stay, (mean) treated infants	25 (46%) Baseline vs 13 (27%) postintervention (*P* not reported) Baseline 16.9 vs postintervention 12.3 d (*P* not reported)[b]	4
Howard et al,[37] 2017	Boston, Massachusetts, 2015-2016	1 Pediatric ward	86	Retrospective cohort	Methadone, buprenorphine, illicit opioid	Morphine, methadone	Parental presence at bedside	Opioid days (mean)	100% parental presence with 8 fewer opioid days $r = -0.34$ (95% CI −0.52 to −0.15)	3
Breastfeeding and Infant Feeding Practices										
Dryden et al,[38] 2009	United Kingdom, 2004-2006	1 Postnatal ward and NICU	450	Case series	Methadone	Morphine	Breastfed for ≥72 h vs <72 h	Infant pharmacologic intervention	Adjusted OR, 0.55 (95% CI, 0.34-0.88), $P = .013$	4
Isemann et al,[39] 2011	Cincinnati, Ohio, 2002-2007	1 NICU	92	Case series	Methadone	Methadone	Percent maternal breastmilk	Opioid days	10% Increase in breastmilk associated with fewer opioid days ($\beta = -0.29$, $P = .005$)	4
Pritham et al,[40] 2012	Maine, 2005-2007	1 NICU	152	Case series	Methadone, buprenorphine	Methadone	Breastmilk only vs mixed feeder vs formula only	Length of stay (mean)	Exclusive breastmilk 3.3 d shorter stay than mixed and 6.6 d shorter than formula only (adjusted $\beta = -3.323$ [SE 1.69], $P = .05$)[d]	4
O'Connor et al,[41] 2013	Maine, 2007-2012	1 Postnatal ward	85	Case series	Buprenorphine	Phenobarbital	Breastfed vs formula fed	Infant pharmacologic intervention, length of stay (mean)	6 (23.1%) vs 15 (30%), $P = .56$ 7.1 (SD 4.4) vs 6.6 d (SD 1.7), $P = .35$[d]	4
Wachman et al,[42] 2013	Maine and Massachusetts, 2011-2012	5 NICUs and level 2 nurseries	86	Prospective cohort	Methadone, buprenorphine	Morphine, methadone	Breastfed vs formula fed[c]	Infant pharmacologic intervention, length of stay (mean)	19 (50%) vs 37 (77%), $P = .009$ 15.8 (95% CI, 11.5-20.1) vs 27.4 d (95% CI, 22.5-32.3)	2
Welle-Strand et al,[43] 2013	Norway, 1999-2009	Neonatal units	124	Retrospective cohort	Methadone, buprenorphine	Diluted tincture of opium	Breastfed vs formula fed	Infant pharmacologic intervention, opioid days (means)	54 (57%) vs 20 (69%) (*P* not significant) 28.6 (SD 19.1) vs 46.7 d (SD 26.3), $P < .05$[d]	4
Short et al,[44] 2016	Pennsylvania, 2012-2014	Multicenter	3725	Population-based cross-Sectional	Not specified	Not specified	Breastfeeding at discharge	Length of stay	9.4% Reduction in stay in breastfed group (adjusted $\beta = -0.060$ [SE 0.031]; $P = .05$)[d]	4

(continued)

Table 2. Studies Examining Nonpharmacologic Care Modalities for the Treatment of Neonatal Abstinence Syndrome (NAS) (continued)

Source	Location and Years of Study	No. of Centers and Setting	No. of Patients	Study Design	In utero Opioid Exposure	Infant Treatment	Intervention or Comparison	Primary Outcome	Findings or Conclusions	Grade[a]
Crook et al,[45] 2017	Wilmington, NC, 2014-2015	1 NICU and pediatric ward	200	Quality improvement initiative	Methadone, illicit, short acting	Not specified	Infant-friendly hospital status and breastfeeding education	Infant pharmacologic intervention, length of stay (mean)	37 (67%) Baseline vs 24 (35%) postintervention ($P < .001$) 18.8 (SD 14.7) baseline vs 10.4 d (SD 10.5) postintervention ($P < .001$)[d]	3
Bogen et al,[46] 2018	Pittsburgh, Pennsylvania, 2010-2012	1 Non-NICU	49	RCT	Methadone	Not specified	Standard (20 kcal/oz) vs high-calorie (24 kcal/oz) formula	Weight gain	Higher mean % weight gain per day in high-calorie group in first 21 d ($\chi^2 = 4316.67$, $P < .001$)	2
Acupuncture										
Raith et al,[47] 2015	Austria, 2009-2014	1 NICU	28	RCT	Opioid substitution	Morphine	Laser acupuncture vs usual care	Opioid days (median)	28 (IQR 22-33) vs 39 d (IQR 32-48), $P = .019$	2
Location of Opioid Taper										
Backes et al,[48] 2012	Columbus, Ohio, 2007-2009	1 Inpatient and outpatient	121	Retrospective cohort	Methadone	Methadone	Inpatient vs outpatient methadone	Length of stay (mean) Opioid days (mean)	25 (SD 15) vs 13 d (SD 5), $P < .01$[d] 21 (SD 14) vs 37 d (SD 20), $P < .01$[d]	3
Smirk et al,[49] 2014	Australia, 2004-2010	1 Inpatient and outpatient	118	Retrospective cohort	Methadone, buprenorphine, polypharmacy	Morphine	Inpatient vs outpatient morphine	Length of stay (mean) Opioid days (mean)	39 (SD 11.8) vs 18.9 d (SD 11.9), $P < .001$[d] Shorter in outpatient group 41 (SD 12.8) vs 36 d (SD 11.0), $P = .02$[d]	3
Kelly et al,[50] 2015	Canada, 2006-2010	2 Inpatient and outpatient	80	Retrospective cohort	Methadone, short-acting	Morphine	Inpatient vs outpatient morphine	Length of stay (median) Opioid days (median)	22 (7-51) vs 16 d (3-54), $P = .04$ 19 (6-48) vs 32 d (12-117), $P = .01$	3
Lee et al,[51] 2015	Plymouth, Pennsylvania, 2007-2013	Multicenter NICU and outpatient	139	Retrospective cohort	Not specified	Methadone, morphine, diluted tincture of opium	Inpatient opioid wean vs outpatient (diluted tincture of opium)	Length of stay (mean)	25.1 (SD 12.3) vs 11.4 d (SD 4.8), $P < .001$[d]	3
Loudin et al,[52] 2017	West Virginia, 2010-2015	1 NICU and outpatient withdrawal center	1023	Retrospective cohort	Not specified	Not specified	NICU vs in-hospital dedicated unit vs outpatient neonatal withdrawal center	Length of stay (median)	24 (IQR 24-52) vs 26 (IQR 26-52) vs 33 (IQR 32-60), P not significant	3
Opioid Weaning Strategies										
Hall et al,[53] 2015	Ohio, 2012-2015	6 NICUs and maternity hospital	360	Retrospective cohort	Methadone, buprenorphine, short-acting	Methadone	Pharmacokinetic-modeled vs standard methadone weans	Opioid days (mean)	13.1 (95% CI 11.4 to 14.9) vs 16.4 d (95% CI 15.2 to 17.5)	3
Hall et al,[54] 2015	Ohio, 2012-2014	6 Children's hospitals and NICUs	981	Retrospective cohort	Not specified	Methadone, morphine	Stringent vs nonstringent weaning protocol	Opioid days (mean)	18.3 (95% CI 15.2 to 21.4) vs 34.0 d (95% CI 29.9 to 38.2)	3
Chisamore et al,[22] 2016	Canada, 2000-2014	1 NICU	146	Retrospective cohort	Methadone, short-acting	Morphine	Weight-based vs symptom-based morphine protocol	Length of stay (median)	6 (IQR, 5-11) vs 15 d (IQR, 8-24), $P < .0001$	3

Abbreviations: HR, heart rate; NICU, newborn intensive care unit; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk. See Table 1, footnote a, for the grading system.

[a] Grading system: 1 = Properly powered and conducted RCT; 2 = well-designed controlled trial without randomization or prospective comparative cohort; 3 = case-control or retrospective cohort; 4 = case series or cross-sectional study; 5 = opinion of respected authorities or case reports.[14]

[b] No measure of variance was available.

[c] Not the primary research question for the research project.

[d] Where 95% CIs were not available, we present SE or SD.

stay (mean, 3- to 17-day reduction), and improved breastfeeding initiation (2-fold increase).[25,31-37,55]

Studies of breastfeeding have similarly demonstrated an association between any amount of breastfeeding and shorter length of hospital stay (mean, 3- to 7-day reduction) and decreased need for pharmacologic treatment (range, 7%-44% reduction). However, all but 1 of these breastfeeding studies were performed retrospectively, and none controlled for whether parents roomed-in.[38-40,44,45] None of the rooming-in or breastfeeding studies were randomized; 10 were single-site studies and 2 were quality improvement initiatives that did not use a formal comparison group.[31,32,34-45] Only 1 of the rooming-in studies[37] attempted to identify the mechanism (for example, swaddling, skin-to-skin contact, breastfeeding, parental presence, reduction of noise levels) by which rooming-in appeared to be associated with the outcomes of interest. The investigators of this study measured the time parents were present at the bedside and found that parental presence for the entirety of the hospitalization was associated with a shorter hospitalization by 9 days ($P < .01$), with 8 fewer days of required opioid therapy ($P < .001$) in comparison to no parental presence.[37]

With regard to infant feeding practices, in an RCT (n = 49; no prespecified sample size) of high-calorie (24 kcal/oz) vs standard-calorie (20 kcal/oz) formula, Bogen et al[46] found no significant differences in maximum percentage weight loss, days to regain birth weight, NAS pharmacologic treatment rates, or length of hospital stay between groups. Infants in the higher-calorie group had a higher mean percentage weight gain per day over the first 21 days of life ($P < .001$).

Acupuncture

A small RCT (n = 28; no prespecified sample size calculations) of laser acupuncture among infants with NAS concurrently receiving pharmacologic treatment found a statistically significant 11-day reduction in opioid treatment days ($P = .019$) in the acupuncture group.[47]

Location and Nature of Opioid Weans

An additional area of recent focus (n = 5) has been the location of pharmacologic treatment, specifically comparing inpatient vs outpatient settings.[48-51] These retrospective analyses found that outpatient weaning protocols were associated with a shorter length of hospitalization, but reported mixed findings regarding total length of opioid treatment.[48-51] One of the studies compared length of stay in a NICU, a dedicated low-stimulation inpatient NAS unit (without the capacity for rooming-in), and an outpatient neonatal withdrawal center. Although this study found no differences in median length of stay, it found significantly lower hospitalization charges in the outpatient group.[52]

All of the location of care studies tracked readmission rates and found no differences in readmission rates or reported adverse events with outpatient care models.[48-51] Two additional retrospective cohort studies found that strict standardization of treatment and weaning protocols, using pharmacokinetic data, was associated with shorter treatment duration.[53,54] One cohort study found that using a weight-based morphine weaning protocol was associated with shorter length of hospitalization than a symptom-based morphine weaning protocol.[22]

Studies Examining Infant Pharmacologic Treatment

Eleven studies (**Table 3**), including 4 RCTs with prespecified sample size calculations, were identified that compared neonatal pharmacologic treatment regimens. These studies measured total opioid treatment days and length of stay as primary outcomes.

Methadone and Morphine

One single-center randomized study (n = 31) by Brown et al[56] compared morphine and methadone and found methadone to be associated with fewer opioid treatment days (median, 14 vs 21 days, $P = .008$). In contrast, in a small retrospective cohort (n = 26), Young et al[58] found that morphine was associated with fewer opioid treatment days compared with methadone. A cohort study by Burke et al[59] (n = 36) found that infants treated with morphine had better Bayley Scales of Infant and Toddler Development scores at 2 months of age compared with infants treated with methadone. Nayeri et al[57] performed an RCT (n = 60, prespecified sample size) comparing morphine vs phenobarbital as first-line pharmacologic treatment and found no difference in mean treatment days.

Buprenorphine

One RCT with a prespecified sample size calculation (n = 63) found that buprenorphine was associated with shorter hospitalization (median 15 vs 28 days, $P < .001$) compared with morphine.[63] A small prospective cohort study (n = 13) found that buprenorphine was associated with shorter hospitalization compared with diluted tincture of opium.[60]

A 2016 multicenter retrospective cohort study (n = 201) by Hall et al[61] compared methadone (n = 163) with buprenorphine (n = 38) among infants exposed to buprenorphine in utero and found shorter length of treatment in the buprenorphine-treated group (mean 9.4 [95% CI, 7.1-11.7] vs 14.0 [95% CI, 12.6-15.4] days, $P < .001$). In another single-center retrospective cohort study by Hall et al[62] (n = 360) with in utero exposures that included methadone, buprenorphine, and short-acting opioids, buprenorphine-treated infants had a shorter duration of treatment (mean 7.4 [95% CI, 6.3-8.5] vs 10.4 days [95% CI, 9.3 to 11.5], $P < .001$) compared with a historical cohort treated with either methadone or morphine.

Clonidine

Four studies, including 2 RCTs with prespecified sample sizes, 1 prospective cohort study, and 1 retrospective cohort study, focused on the use of clonidine as either first-line or adjunctive therapy. The studies examined varying clonidine treatment regimens and found conflicting results. The RCT by Agthe et al[64] (n = 80), which compared adjunctive clonidine vs placebo in infants who were all receiving diluted tincture of opium as first-line treatment, found that the adjunctive clonidine group had shorter diluted tincture of opium treatment days in comparison with diluted tincture of opium alone (median 11 vs 15 days, $P = .02$).

A second RCT (n = 68) by Surran et al[65] found that adjunctive clonidine was associated with more morphine treatment days in comparison to adjunctive phenobarbital (18.2 vs 13.6 days, mean difference −4.6 days; 95% CI, −0.3 to −8.9). Devlin et al[67] performed a retrospective cohort study (n = 190) comparing use of

Table 3. Studies Examining Infant Pharmacologic Treatment Regimens for Neonatal Abstinence Syndrome

Source	Location and Years of Study	No. of Centers and Setting	No. of Patients	Study Design	In utero Opioid Exposure	Assessment	Intervention	Comparison	Primary Outcome	Findings or Conclusions (Intervention vs Comparison)	Grade[a]
Methadone and Morphine											
Brown et al,[56] 2015	Bangor, Maine, 2011-2012	1NICU	31	RCT	Methadone, buprenorphine	Finnegan scale	Methadone	Morphine	Opioid days (median)	14 vs 21 d, P = .008	1
Nayeri et al,[57] 2015	Iran, 2009-2014	2 Not specified	60	RCT	Opium, heroin, methadone	Finnegan scale	Morphine	Phenobarbital	Treatment days (mean)	8.5 (SD 5) vs 8.5 d (SD 4), P = .09[b]	1
Young et al,[58] 2015	Columbus, Ohio, 2010-2011	1 NICU	26	Retrospective cohort	Not specified	Finnegan scale	Methadone	Morphine	Length of stay (mean)	44.2 (SD 28.0) vs 12.1 d (SD 4.6)[b]	3
Burke and Beckwith,[59] 2017	New Brunswick, New Jersey, 2017	1 Rehabilitation hospital	36	Retrospective cohort	Not specified	Finnegan scale	Morphine	Methadone	BSID at 46-50 d (mean)	Cognitive scores (91.3 [SD 9.8] vs 83.0 [SD 11.9]; P = .03) Motor scores (96.3 [SD 5.7] vs 89.6 [SD 9.1]; P = .01)[b]	3
Buprenorphine											
Kraft et al,[60] 2008	Philadelphia, Pennsylvania, 2005-2008	1 Not specified	13	Prospective cohort	Methadone	Modified Finnegan scale	Buprenorphine	Diluted tincture of opium	Opioid days (mean)	22 (SD 11) vs 32 d (SD 16), P = .08[b]	2
Hall et al,[61] 2016	Ohio, 2012-2014	6 NICU and nursery	201	Retrospective cohort	Buprenorphine, short acting	Finnegan scale	Buprenorphine	Methadone	Opioid days (mean)	9.4 (95% CI, 7.1-11.7) vs 14.0 d (95% CI, 12.6-15.4)	3
Hall et al,[62] 2017	Kentucky, 2013-2017	1 Not specified	360	Retrospective cohort	Methadone, buprenorphine, short-acting	Finnegan scale	Buprenorphine	Methadone, morphine	Opioid days (mean) Length of stay (mean)	7.4 (95% CI, 6.3-8.5) vs 10.4 d (95% CI, 9.3-11.5), P < .001 12.4 (95% CI, 11.3-13.6) vs 15.2 d (95% CI, 14.1-16.4), P < .001	3
Kraft et al,[63] 2017	Philadelphia, Pennsylvania, 2011-2016	1 Not specified	63	RCT	Methadone, buprenorphine	MOTHER scale	Buprenorphine	Morphine	Opioid days (median)	15 (3-67) vs 28 d (13-67), P < .001	1
Clonidine											
Agthe et al,[64] 2009	Baltimore, Maryland, 2002-2005	2 Transitional care unit	80	RCT	Methadone, heroin	Modified Finnegan scale	Diluted tincture of opium + clonidine	Diluted tincture of opium + placebo	Opioid days (mean)	11 (95% CI, 8-15) vs 15 d (95% CI, 12-47)	1
Surran et al,[65] 2013	Springfield, Massachusetts, 2010-2012	1 NICU	68	RCT	Methadone, buprenorphine, oxycodone	Modified Finnegan scale	Morphine + clonidine	Morphine + phenobarbital	Opioid days (mean)	Shorter in phenobarbital group 18.2 (95% CI, 14.9-21.5) vs 13.6 d (95% CI, 11.0-16.1)	1
Bada et al,[66] 2015	Lexington, Kentucky, 2015	1 NICU	31	Prospective cohort	Methadone, buprenorphine, short-acting	Finnegan scale	Clonidine	Morphine	Opioid days (median) NNNS at 1-2 mo BSID at 1 y	28 (18-107) vs 39 d (26-89), P = .02 Mean lethargy score 5.13 (SD 2.12) vs 3.6 (SD 1.6)[b] No differences in BSID	2
Devlin et al,[67] 2017	Louisville, Kentucky, 2005-2015	1 Not specified	190	Retrospective cohort	Methadone, buprenorphine, short-acting	Finnegan scale	Morphine every 4 h + phenobarbital	Morphine every 3 h + clonidine	Opioid days (mean) Length of stay (mean)	35 vs 26.5 d (95% CI, 4.5-12), P < .001 42 vs 33 d (95% CI, 5.1-13), P < .001)	3

Abbreviations: BSID, Bailey Scales of Infant and Toddler Development – Third Edition; NICU, neonatal intensive care unit; NNNS, NICU Network Neurobehavioral Scale; RCT, randomized clinical trial.

[a] Grading system: 1 = Properly powered and conducted RCT; 2 = well-designed controlled trial without randomization or prospective comparative cohort; 3 = case-control or retrospective cohort; 4 = case series or cross-sectional study; 5 = opinion of respected authorities or case reports.[14]

[b] Where 95% CIs were not available, we present SE or SD. Given the correlation between days of opioid treatment and length of stay, we report only opioid treatment days when both were reported in the studies.

Table 4. Studies Examining Maternal Pharmacologic Treatment Regimens on Infant Outcomes in Neonatal Abstinence Syndrome

Source	Location and Years of Study	No. of Centers and Setting	No. of Patients	Study Design	Infant Treatment	Assessment	Intervention	Comparison	Primary Outcome	Findings or Conclusions (Intervention vs Comparison)	Grade[a]
Binder and Vavrinková,[68] 2008	Czech Republic, 2002-2007	1 Not specified	70	RCT	Diluted tincture of opium	Finnegan	Methadone	Buprenorphine	Finnegan scores (average over time)	(17.8) vs Buprenorphine (9.2), $P < .001$[b]	2
Jones et al,[30] 2010	US, Austria, Canada, 2005-2008	8 Not specified	131	RCT	Morphine	MOTHER scale	Methadone	Buprenorphine	Opioid days (mean)	Buprenorphine group had fewer opioid days 9.9 (SD 1.6) vs 4.1 d (SD 1.0), $P < .003$[c]	1
Bier et al,[69] 2015	New Bedford, Massachusetts, 1995-2014	1 Level 2 nursery	220	Retrospective cohort	Diluted tincture of opium, morphine, phenobarbital	Finnegan	Methadone	Buprenorphine	BSID at 4 mo AIMS at 4 mo (mean)	No differences in BSID High-dose methadone (38.1; SD 24) vs lower-dose methadone (44.8; SD 24) vs buprenorphine (53.5; SD 23), $P < .025$[c]	3
Whitham et al,[70] 2015	Australia, 2002-2006	2 Outpatient centers	32 Opioid 10 controls	Prospective cohort	Not specified	Finnegan	Methadone	Buprenorphine	VEPs at 36 mo	No differences in the 53% that completed follow-up	2

Abbreviations: AIMS, Alberto Infant Motor Scale; BSID, Bailey Scale of Infant and Toddler Development – Third Edition; NICU, neonatal intensive care unit; RCT, randomized clinical trial; VEPs, visual evoked potentials.

[a] Grading system: 1 = Properly powered and conducted RCT; 2 = well-designed controlled trial without randomization or prospective comparative cohort; 3 = case-control or retrospective cohort; 4 = case series or cross-sectional study; 5 = opinion of respected authorities or case reports.[14]

[b] No measure of variance was available.

[c] Where 95% CIs were not available, we presented SE or SD.

adjunctive clonidine with an every-3-hour morphine dosing protocol with adjunctive phenobarbital with an every-4-hour morphine protocol. They found that the group that received adjunctive clonidine had shorter opioid treatment days (mean difference 8.5 days, 95% CI, 4.5 to 12).

A prospective cohort study (n = 31) by Bada et al[66] compared clonidine vs morphine as primary treatment and found shorter treatment days in the clonidine group. This study also examined neurodevelopmental outcomes and found higher mean lethargy scores on the NICU Network Neurobehavioral Scale in the clonidine group in the first 2 months of life; however, no differences in Bayley Scales of Infant and Toddler Development scores were detected when the infants were reexamined at 1 year of age.

Studies Examining Maternal Pharmacologic Treatment

There was 1 RCT with a prespecified sample size calculation examining the effect of maternal treatment regimens on NAS severity.[30] In this multicenter RCT (n = 131), entitled the MOTHER study, pregnant women were randomized to receive methadone or buprenorphine (**Table 4**). Investigators found that buprenorphine was associated with fewer opioid treatment days (mean 4.1 vs 9.9 days, $P < .003$).[30] A second RCT by Binder and Vavrinková[68] randomized 70 pregnant women to receive methadone or buprenorphine. Infant Finnegan scores were averaged over time and found to be lower among infants whose mothers were treated with buprenorphine (9.2 vs 17.8, $P < .001$).

Two cohort studies examined differences in neurodevelopmental outcomes as a function of maternal treatment regimens. A retrospective study by Bier et al[69] compared infants whose mothers received buprenorphine vs methadone (n = 220) and found no differences in BSID scores at 4 months of age. The second cohort study prospectively examined the association between in utero opioid exposure and changes in visual outcomes, finding no differences in visual evoked potentials at 36 months of age between infants whose mothers were treated with methadone vs buprenorphine.[70]

Discussion

Fifty-three articles pertaining to the diagnosis and management of infants with NAS published in the last decade were selected for review. Regarding assessment and diagnosis, there have been a number of studies of novel diagnostic modalities that attempt to correlate physiologic parameters such as heart rate and skin conductance with subsequent symptomatic withdrawal; however, none of these modalities has been studied in large samples, and none has significantly affected clinical practice.[5] The Finnegan tool was used most commonly in the studies reviewed, but it lacks internal consistency, and there have been few studies of interrater reliability. A newer assessment method[25,29] that uses the infant's ability to eat, sleep, and be consoled requires further standardization and validation and has yet to be correlated with long-term outcomes.

The most clinically meaningful interventions in NAS management pertain to nonpharmacologic care—specifically, interventions that promote parental rooming-in and breastfeeding. These nonpharmacologic interventions are heterogeneous and they

have largely been studied either retrospectively with a comparison group, or prospectively without one. The retrospective analyses have tended to use data that were not collected specifically for the purpose of intervention evaluation. Despite this, data from these studies suggest that nonpharmacologic interventions may decrease the need for opioid replacement treatment and result in shorter hospitalizations. Because rooming-in interventions typically reflect a change in a hospital's overall care model, studies pertaining to them tend only to exclude infants who are preterm or who have other acute medical issues, without exclusions having been made for maternal characteristics such as continued illicit drug use. The results of individual rooming-in studies summarized in this review are consistent with a recently published meta-analysis by MacMillan and colleagues.[71] The meta-analysis, which included 6 studies of rooming-in, 5 of which are included in this review, found a risk ratio for pharmacologic treatment of 0.37 (95% CI, 0.19 to 0.71) for rooming-in models of care and nonpharmacologic care approaches, when compared with standard approaches to care.[71]

Regarding infant pharmacologic interventions, only 4 clinical trials with prespecified sample sizes have been published; each uses length of hospital stay as the primary outcome. There is currently inconclusive evidence to recommend one pharmacologic treatment regimen over another, although buprenorphine was consistently associated with shorter length of stay across 4 studies (1 RCT and 3 cohort studies) including a total of 258 buprenorphine-treated infants.[60-63] Methadone, morphine, and buprenorphine are the most commonly studied first-line pharmacologic agents, with current available evidence not definitively favoring one agent over another; clinical trials comparing these agents are ongoing (eTable 1 in the Supplement). For second-line therapy, phenobarbital or clonidine are the most commonly studied agents, with conflicting evidence as to which medication results in fewer opioid-treatment days. There is minimal evidence regarding the differential effects of the various infant treatment modalities on infant neurodevelopmental outcomes.

Studies of maternal treatment regimens have found that buprenorphine treatment for the mother results in less pharmacologic treatment and shorter hospitalizations for the infant, yet women receiving buprenorphine in one study were almost twice as likely to drop out of treatment compared with those receiving methadone.[30] These findings are consistent with a 2014 meta-analysis by Brogly et al[72] (which included the RCT by Jones et al[30]) that concluded that maternal buprenorphine treatment is associated with less NAS medication treatment and shorter length of hospital stay compared with maternal treatment with methadone. Data concerning the effects of maternal treatment modalities on infant neurodevelopmental outcomes remain inconclusive.

This review identified important limitations in the available NAS literature. First, the preponderance of evidence is based on low-quality studies that are uncontrolled, use single-center or retrospective data, have small sample sizes, or use quality improvement methodologies not designed for generalizability. Second, the nonrandomized studies inadequately account for the myriad maternal exposures, including polypharmacy exposure, which has become increasingly common and is associated with both short-term and long-term outcomes.[73,74] Third, analyses of pharmacologic interventions tend not to account for concurrent nonpharmacologic care measures which, as suggested in the rooming-in and breastfeeding studies, may exert substantial effects. Although in the context of a randomized study such nonpharmacologic factors as rooming-in and breastfeeding should be evenly distributed across randomization groups, these factors can instill external validity or modify the effect of medication therapy.

Fourth, the variability in length of opioid treatment and hospital stay, seen even across the studies of common opioid comparators, suggests substantial center effects and raises the possibility that single-center studies may be inadequate to produce generalizable results concerning NAS treatment. Fifth, nearly all treatment studies used the Finnegan scale or some modified version of it, which has been shown to have poor internal consistency.[19] Sixth, almost all studies only included late preterm and term infants, which is a limitation given that 21% to 29% of infants with in utero opioid exposure are born preterm.[68]

Seventh, almost all studies examined intermediate outcomes such as hospital length of stay, length of opioid therapy, or need for pharmacologic treatment. Although length of stay is an important measure, and it is likely better that infants be cared for at home, there is currently no evidence that links such intermediate outcomes with true health outcomes such as neurodevelopment, and there is a theoretical risk that discharging families at high social risk too early may be associated with increased harm. Eighth, existing studies assessing neurodevelopmental outcomes often lack details of NAS treatment and do not adequately account for important maternal sociodemographic factors, addiction severity, and psychiatric comorbidities.

In addition to the above limitations, there remains a lack of clarity in how to best characterize infants with opioid exposure; and there is a lack of standardization on whether to give opioid-exposed infants who do not require pharmacologic treatment

Box. Current Research Gaps in Neonatal Abstinence Syndrome

Diagnosis
- Development of a valid assessment tool for determining the need for pharmacologic treatment
- Further development of physiologic markers to determine the need for pharmacologic treatment

Nonpharmacologic Care
- Need for well-designed prospective studies of the efficacy of various nonpharmacologic approaches, including examining of the various elements of rooming-in
- Need for intervention studies examining ways to improve aspects of nonpharmacologic care such as breastfeeding

Pharmacologic Care
- Further study of the use of buprenorphine as first-line pharmacologic treatment for infants with varied prenatal exposures
- Further study of the use of clonidine as a primary or adjunctive agent
- Further study of the safety of outpatient management of opioid weans

Long-term Outcomes
- Need for prospective studies that adequately control for prenatal exposures, neonatal abstinence syndrome management, and parental sociodemographic factors

a diagnosis of NAS. With current efforts promoting nonpharmacologic care reducing the number of infants who require pharmacologic treatment, this has important implications for epidemiologic research and public health surveillance.

What appears to be clear is that when safe and feasible, infants with NAS should be cared for outside of an intensive care unit; they should room-in with their parents; and they should be breastfed if there are no contraindications. Areas of uncertainty, however, include how best to assess when to begin medication therapy; what the optimal medication treatment regimen is (type and dosing frequency); what is the best location is to wean medications (outpatient vs inpatient); and whether any of these management trade-offs is associated with long-term neurodevelopmental or family outcomes (Box).

Given the national opioid crisis, there is a need for more research on the opioid-exposed mother-infant dyad. This research needs to augment quality improvement work that has been published over the past 5 years with RCTs and longitudinal analyses that measure individual and family-level outcomes and go beyond process measures such as length of hospital stay. Additionally, the individual components of nonpharmacologic interventions need to be understood, so that the research and clinical communities can understand their mechanisms of action and tailor such interventions to local contexts without sacrificing impact.

Conclusions

The management of NAS has evolved over the past 10 years, with new focus on nonpharmacologic management strategies. However, available evidence is based on small or low-quality studies that focus on intermediate hospital outcomes. Clinical trials and longitudinal studies are needed to evaluate health and neurodevelopmental outcomes associated with objective diagnostic approaches and pharmacologic and nonpharmacologic treatment modalities.

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REFERENCES

1. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag*. 2009;5(1):47-55.

2. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2):e540-e560. doi:10.1542/peds.2011-3212

3. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol*. 2015;35(8):667. doi:10.1038/jp.2015.63

4. Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of neonatal abstinence syndrome—28 states, 1999-2013. *MMWR Morb Mortal Wkly Rep*. 2016;65(31):799-802. doi:10.15585/mmwr.mm6531a2

5. Bogen DL, Whalen BL, Kair LR, Vining M, King BA. Wide variation found in care of opioid-exposed newborns. *Acad Pediatr*. 2017;17(4):374-380. doi:10.1016/j.acap.2016.10.003

6. Milliren CE, Gupta M, Graham DA, Melvin P, Jorina M, Ozonoff A. Hospital variation in neonatal abstinence syndrome incidence, treatment modalities, resource use, and costs across pediatric hospitals in the United States, 2013 to 2016. *Hosp Pediatr*. 2018;8(1):15-20.

7. Oei JL, Melhuish E, Uebel H, et al. Neonatal abstinence syndrome and high school performance. *Pediatrics*. 2017;139(2):e20162651. doi:10.1542/peds.2016-2651

8. Nygaard E, Moe V, Slinning K, Walhovd KB. Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatr Res*. 2015;78(3):330-335. doi:10.1038/pr.2015.95

9. Konijnenberg C, Melinder A. Executive function in preschool children prenatally exposed to methadone or buprenorphine. *Child Neuropsychol*. 2015;21(5):570-585. doi:10.1080/09297049.2014.967201

10. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1-2):141-158.

11. Grossman M, Seashore C, Holmes AV. Neonatal abstinence syndrome management: a review of recent evidence. *Rev Recent Clin Trials*. 2017;12(4):226-232. doi:10.2174/1574887112666170816144818

12. McQueen K, Murphy-Oikonen J. Neonatal abstinence syndrome. *N Engl J Med*. 2016;375(25):2468-2479. doi:10.1056/NEJMra1600879

13. Klaman SL, Isaacs K, Leopold A, et al. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: literature review to support national guidance. *J Addict Med*. 2017;11(3):178-190. doi:10.1097/ADM.0000000000000308

14. Howick J, Chalmers I, et al; Oxford Centre for Evidence-Based Medicine. *Levels of Evidence*. https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf. Accessed March 3, 2018.

15. Kistin C, Silverstein M. Pilot studies: a critical but potentially misused component of interventional research. *JAMA*. 2015;314(15):1561-1562. doi:10.1001/jama.2015.10962

16. Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. *Ann Intern Med*. 2012;156(1 pt 1):37. doi:10.7326/0003-4819-156-1-201201030-00006.

17. Maguire D, Cline GJ, Parnell L, Tai C-Y. Validation of the Finnegan neonatal abstinence syndrome tool-short form. *Adv Neonatal Care*. 2013;13(6):430-437. doi:10.1097/ANC.0000000000000033

18. Nagiub M, Alton K, Avula V, Hagglund K, Anne P. Heart rate variability evaluation in the assessment and management of in-utero drug-exposed infants. *SAGE Open Med*. 2014;2:2050312114556525. doi:10.1177/2050312114556525

19. Jones HE, Seashore C, Johnson E, et al. Psychometric assessment of the Neonatal Abstinence Scoring System and the MOTHER NAS Scale. *Am J Addict*. 2016;25(5):370-373. doi:10.1111/ajad.12388

20. Jansson LM, Dipietro JA, Elko A, Velez M. Maternal vagal tone change in response to methadone is associated with neonatal abstinence syndrome severity in exposed neonates. *J Matern Fetal Neonatal Med*. 2007;20(9):677-685. doi:10.1080/14767050701490327

21. Leeman LM, Brown SA, Albright B, Skipper B, Hsi A, Rayburn WF. Association between intrapartum fetal heart rate patterns and neonatal abstinence syndrome in methadone exposed neonates. *J Matern Fetal Neonatal Med*. 2011;24(7):955-959. doi:10.3109/14767058.2010.536863

22. Chisamore B, Labana S, Blitz S, Ordean A. A comparison of morphine delivery in neonatal opioid withdrawal. *Subst Abuse*. 2016;10(suppl 1):49-54. doi:10.4137/SART.S34550

23. Jones HE, Seashore C, Johnson E, Horton E, O'Grady KE, Andringa K. Measurement of neonatal abstinence syndrome: evaluation of short forms. *J Opioid Manag*. 2016;12(1):19-23. doi:10.5055/jom.2016.0308

24. 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;105(3):e99-e106. doi:10.1111/apa.13287

25. Grossman MR, Berkwitt AK, Osborn RR, et al. An initiative to improve the quality of care of infants

with neonatal abstinence syndrome. *Pediatrics*. 2017;139(6):e20163360. doi:10.1542/peds.2016-3360

26. Isemann BT, Stoeckle EC, Taleghani AA, Mueller EW. Early prediction tool to identify the need for pharmacotherapy in infants at risk of neonatal abstinence syndrome. *Pharmacotherapy*. 2017;37(7):840-848. doi:10.1002/phar.1948

27. Oji-Mmuo CN, Gardner FC, Doheny KK. Heightened sympathetic arousal is demonstrated by skin conductance responsivity to auditory stimuli in a small cohort of neonates with opiate withdrawpal [published online June 15, 2017]. *Brain Res Bull*. doi:10.1016/j.brainresbull.2017.06.007

28. Subedi L, Huang H, Pant A, et al. Plasma brain-derived neurotrophic factor levels in newborn infants with neonatal abstinence syndrome. *Front Pediatr*. 2017;5:238. doi:10.3389/fped.2017.00238

29. Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A novel approach to assessing infants with neonatal abstinence syndrome. *Hosp Pediatr*. 2018;8(1):1-6. doi:10.1542/hpeds.2017-0128

30. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320-2331. doi:10.1056/NEJMoa1005359

31. 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;53(10):1722-1730.

32. Abrahams RR, MacKay-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;32(9):866-871.

33. Saiki T, Lee S, Hannam S, Greenough A. Neonatal abstinence syndrome: postnatal ward versus neonatal unit management. *Eur J Pediatr*. 2010;169(1):95-98. doi:10.1007/s00431-009-0994-0

34. Hünseler C, Brückle M, Roth B, Kribs A. Neonatal opiate withdrawal and rooming-in: a retrospective analysis of a single center experience. *Klin Padiatr*. 2013;225(5):247-251. doi:10.1055/s-0033-1347190

35. Newman A, Davies GA, Dow K, et al. Rooming-in care for infants of opioid-dependent mothers: implementation and evaluation at a tertiary care hospital. *Can Fam Physician*. 2015;61(12):e555-e561.

36. Holmes AV, Atwood EC, Whalen B, et al. Rooming-in to treat neonatal abstinence syndrome: improved family-centered care at lower cost. *Pediatrics*. 2016;137(6):e20152929. doi:10.1542/peds.2015-2929

37. Howard MB, Schiff DM, Penwill N, et al. Impact of parental presence at infants' bedside on neonatal abstinence syndrome. *Hosp Pediatr*. 2017;7(2):63-69. doi:10.1542/hpeds.2016-0147

38. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. 2009;116(5):665-671. doi:10.1111/j.1471-0528.2008.02073.x

39. Isemann B, Meinzen-Derr J, Akinbi H. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. *J Perinatol*. 2011;31(1):25-29. doi:10.1038/jp.2010.66

40. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstet Gynecol neonatal Nurs JOGNN*. 2012;41(2):180-190. doi:10.1111/j.1552-6909.2011.01330.x.

41. O'Connor AB, Collett A, Alto WA, O'Brien LM. Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy. *J Midwifery Womens Health*. 2013;58(4):383-388. doi:10.1111/jmwh.12009

42. Wachman EM, Hayes MJ, Brown MS, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *JAMA*. 2013;309(17):1821-1827. doi:10.1001/jama.2013.3411

43. 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;102(11):1060-1066. doi:10.1111/apa.12378

44. Short VL, Gannon M, Abatemarco DJ. The association between breastfeeding and length of hospital stay among infants diagnosed with neonatal abstinence syndrome: a population-based study of in-hospital births. *Breastfeed Med*. 2016;11:343-349. doi:10.1089/bfm.2016.0084

45. Crook K, Brandon D. Prenatal breastfeeding education: impact on infants with neonatal abstinence syndrome. *Adv Neonatal Care*. 2017;17(4):299-305. doi:10.1097/ANC.0000000000000392

46. Bogen DL, Hanusa BH, Baker R, Medoff-Cooper B, Cohlan B. Randomized clinical trial of standard- versus high-calorie formula for methadone-exposed infants: a feasibility study. *Hosp Pediatr*. 2018;8(1):7-14. doi:10.1542/hpeds.2017-0114

47. Raith W, Schmölzer GM, Resch B, et al. Laser acupuncture for neonatal abstinence syndrome: a randomized controlled trial. *Pediatrics*. 2015;136(5):876-884. doi:10.1542/peds.2015-0676

48. 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;32(6):425-430. doi:10.1038/jp.2011.114

49. 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;103(6):601-604. doi:10.1111/apa.12603

50. 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;17(2):151-157. doi:10.1007/s40272-014-0096-y

51. Lee J, Hulman S, Musci M Jr, Stang E. Neonatal abstinence syndrome: influence of a combined inpatient/outpatient methadone treatment regimen on the average length of stay of a Medicaid NICU population. *Popul Health Manag*. 2015;18(5):392-397. doi:10.1089/pop.2014.0134

52. Loudin S, Werthammer J, Prunty L, Murray S, Shapiro JI, Davies TH. A management strategy that reduces NICU admissions and decreases charges from the front line of the neonatal abstinence syndrome epidemic. *J Perinatol*. 2017;37(10):1108-1111. doi:10.1038/jp.2017.101

53. Hall ES, Meinzen-Derr J, Wexelblatt SL. Cohort analysis of a pharmacokinetic-modeled methadone weaning optimization for neonatal abstinence syndrome. *J Pediatr*. 2015;167(6):1221. doi:10.1016/j.jpeds.2015.09.038

54. Hall ES, Wexelblatt SL, Crowley M, et al; OCHNAS Consortium. Implementation of a neonatal abstinence syndrome weaning protocol: a multicenter cohort study. *Pediatrics*. 2015;136(4):e803-e810. doi:10.1542/peds.2015-1141

55. Hodgson ZG, Abrahams RR. A rooming-in program to mitigate the need to treat for opiate withdrawal in the newborn. *J Obstet Gynaecol Can*. 2012;34(5):475-481.

56. Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol*. 2015;35(4):278-283. doi:10.1038/jp.2014.194

57. Nayeri F, Sheikh M, Kalani M, et al. Phenobarbital versus morphine in the management of neonatal abstinence syndrome, a randomized control trial. *BMC Pediatr*. 2015;15:57. doi:10.1186/s12887-015-0377-9

58. Young ME, Hager SJ, Spurlock D. Retrospective chart review comparing morphine and methadone in neonates treated for neonatal abstinence syndrome. *Am J Heal Pharm*. 2015;72(23 suppl 3):S162-S167. doi:10.2146/sp150025

59. Burke S, Beckwith AM. Morphine versus methadone treatment for neonatal withdrawal and impact on early infant development[published online July 25, 2017]. *Glob Pediatr Heal*. doi:10.1177/2333794X1772112

60. Kraft WK, Gibson E, Dysart K, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. *Pediatrics*. 2008;122(3):e601-e607. doi:10.1542/peds.2008-0571

61. Hall ES, Isemann BT, Wexelblatt SL, et al. A cohort comparison of buprenorphine versus methadone treatment for neonatal abstinence syndrome. *J Pediatr*. 2016;170:39-44. doi:10.1016/j.jpeds.2015.11.039

62. Hall ES, Rice WR, Folger AT, Wexelblatt SL. Comparison of neonatal abstinence syndrome treatment with sublingual buprenorphine versus conventional opioids. *Am J Perinatol*. November 2017. doi:10.1055/s-0037-1608634

63. Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. *N Engl J Med*. 2017;376(24):2341-2348. doi:10.1056/NEJMoa1614835

64. Agthe AG, Kim GR, Mathias KB, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. 2009;123(5):e849-e856. doi:10.1542/peds.2008-0978

65. 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;33(12):954-959. doi:10.1038/jp.2013.95

66. Bada HS, Sithisarn T, Gibson J, et al. Morphine versus clonidine for neonatal abstinence syndrome. *Pediatrics*. 2015;135(2):e383-e391. doi:10.1542/peds.2014-2377

67. Devlin LA, Lau T, Radmacher PG. Decreasing total medication exposure and length of stay while completing withdrawal for neonatal abstinence syndrome during the neonatal hospital stay. *Front Pediatr*. 2017;5:216. doi:10.3389/fped.2017.00216

68. Binder T, Vavrinková B. Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department. *Neuro Endocrinol Lett*. 2008;29(1):80-86.

69. Bier JB, Finger AS, Bier BA, Johnson TA, Coyle MG. Growth and developmental outcome of infants with in-utero exposure to methadone vs buprenorphine. *J Perinatol*. 2015;35(8):656-659. doi:10.1038/jp.2015.22

70. Whitham JN, Spurrier NJ, Baghurst PA, Weston P, Sawyer MG. Visual evoked potential latencies of three-year-old children prenatally exposed to buprenorphine or methadone compared with non-opioid exposed children: the results of a longitudinal study. *Neurotoxicol Teratol*. 2015;52(pt A):17-24. doi:10.1016/j.ntt.2015.09.008

71. MacMillan KDL, Rendon CP, Verma K, Riblet N, Washer DB, Volpe Holmes A. Association of rooming-in with outcomes for neonatal abstinence syndrome: a systematic review and meta-analysis [published online February 5, 2018]. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2017.5195

72. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. *Am J Epidemiol*. 2014;180(7):673-686. doi:10.1093/aje/kwu190

73. Reddy UM, Davis JM, Ren Z, Greene MF; Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop Invited Speakers. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstet Gynecol*. 2017;130(1):10-28. doi:10.1097/AOG.0000000000002054

74. Huybrechts KF, Bateman BT, Desai RJ, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *BMJ*. 2017;358:j3326.