

# A Meta-Analysis of Breastfeeding Effects for Infants With Neonatal Abstinence Syndrome

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**Background:** Neonatal abstinence syndrome (NAS) rates have dramatically increased. Breastfeeding is a nonpharmacological intervention that may be beneficial, reducing NAS symptom severity and thus the need for and duration of pharmacological treatment and length of hospital stay.

**Objectives:** Conduct meta-analysis to determine whether breastfeeding results in better outcomes for NAS infants. Variables included symptom severity, need for and duration of pharmacological treatment, and length of hospital stay.

**Methods:** PubMed, Scopus, Embase, and Cochrane Library were searched from 2000 to 2020, and comparative studies examining breastfeeding for NAS infants were extracted. Randomized trials and cohort studies were included. Data were extracted and evaluated with Review Manager Version 5.3. A random-effects model was used to pool discontinuous outcomes using risk ratio and 95% confidence intervals. Continuous outcomes were evaluated by mean differences and 95% confidence intervals.

**Results:** Across 11 studies, 6,375 neonates were included in the meta-analysis. Using a random-effects analysis, breastfeeding reduced initiation of pharmacological treatment, reduced duration of pharmacological treatment, and reduced length of stay. No differences were detected for severity of NAS symptoms. Most studies only reported one to two variables of interest. For most studies, these variables were not the primary study outcomes. All studies were found to be of low risk and good quality based on the Cochrane Risk Assessment Tools. Varying breastfeeding definitions limit generalizability.

**Discussion:** Breastfeeding is associated with decreased initiation and duration of pharmacological treatment and length of stay.

**Key Words:** breastfeeding • methadone • neonatal abstinence syndrome • opioid-related disorders • review

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As opioid use in pregnant women in the United States persists, the associated condition of neonatal abstinence syndrome (NAS) has become an important issue worldwide, leading to increasing hospital costs (Winkelman et al., 2018), prolonged hospitalizations (Devlin et al., 2017; Parlett et al., 2019), and more complex health problems in newborns and early childhood (Kraft et al., 2016). NAS is characterized by repeated exposure to substances such as opioids prebirth, discontinuing exposure postbirth, and subsequent infant withdrawal (Patrick et al., 2016). Withdrawal can occur following the use of both illicit opioids and prescription opioids, including the medication-assisted treatment (MAT) used to manage opioid use disorder (i.e., methadone or buprenorphine; Ko et al., 2016). NAS typically involves myriad symptoms such as a high-pitched, inconsolable cry; tremors; and issues associated with gastrointestinal distress, like feeding difficulties (Ko et al., 2016; Mangat et al., 2019).

Withdrawal from prenatal opioid exposure is anticipated; however, the level and severity of withdrawal symptoms are unpredictable (Ko et al., 2016). To date, assessment of NAS symptom severity is subjective (no available objective tests), thus limiting diagnostic clarity. To improve standardization, the Finnegan Neonatal Abstinence Scoring System Tool (FNAST) is routinely used within U.S. hospitals (Devlin et al., 2020). The FNAST is used to assess gastrointestinal, neurological,

and autonomic withdrawal symptoms and is based on a cumulative score from 30 items that attempts to quantify the severity of withdrawal (Devlin et al., 2020).

Little is known about contributing factors associated with NAS symptom severity (Wachman, Schiff, & Silverstein, 2018). Nonetheless, treatment guidelines specify that if NAS symptoms progress, pharmacological intervention is required and should be initiated (Section on Breastfeeding, 2012). Pharmacological management, including the use of oral morphine sulfate, methadone hydrochloride, and buprenorphine, is most often predicated on changes in FNAST scores over time (Brogly et al., 2018; Patrick et al., 2016; Wachman, Grossman et al., 2018). Despite the importance of pharmacological intervention, this approach often leads to a lengthy hospital stay, the need for extensive nursing care, and prolonged mother-infant separation (Patrick et al., 2016).

Although standardized pharmacological management protocols may improve outcomes, the role of nonpharmacological management in reducing withdrawal symptoms remains unclear (Arter et al., 2021). It is important to note that some evidence suggests that initiation of and continued breastfeeding is commonly used as a nonpharmacological approach to decrease the severity of NAS symptoms (Mangat et al., 2019; Wu & Carre, 2018); this consequentially reduces the need for ongoing pharmacological management. Therefore, breastfeeding is recommended by the American Academy of Pediatrics for mothers receiving MAT and their infants (Section on Breastfeeding, 2012).

Since 2013, eight literature reviews have been published regarding breastfeeding outcomes for infants with NAS (Cirillo & Francis, 2016; Clark, 2019; Holmes et al., 2017; MacVicar & Kelly, 2019; McQueen et al., 2019; Pritham, 2013; Ryan et al., 2019; Wu & Carre, 2018; see Table 1). Four of these reviews were published in 2019, highlighting the growing importance of breastfeeding to standard of care (Clark, 2019; MacVicar & Kelly, 2019; McQueen et al., 2019; Ryan et al., 2019). Many published reviews include analysis of the same studies, but each review's focus is somewhat different. Several of the reviews focused specifically on breastfeeding or human milk, whereas others concentrated on the effects of breastfeeding, among other nonpharmacological soothing techniques.

To date, no meta-analyses of the existing literature on breastfeeding and NAS have been published. This represents a significant gap because meta-analysis allows for the quantitative, formal, and systematic assessment of the results of previous research to derive conclusions about the quality of the evidence. Therefore, the purpose of this meta-analysis was to determine whether breastfeeding results in improved outcomes for infants with NAS when compared to infants who were not breastfed or did not receive expressed human milk. Severity of NAS symptoms, initiation, and duration of pharmacological treatment, as well as length of hospital stay (LOS), were the four variables of interest considered for this meta-analysis.

## METHODS

### Review Protocol

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards (Moher et al., 2009). Included in this review were randomized clinical trials and comparative cohort studies of infants with the diagnosis of NAS, where breastfeeding was included as the main variable of interest. Prenatal opioid exposure prescription included prescription opioids, heroin, and prescribed or illicitly obtained methadone or buprenorphine, although many infants experienced prenatal polysubstance exposure. For the included studies, breastfeeding often included the receipt of expressed human milk.

Criteria for inclusion were studies that were published between 2006 and 2020 (last 15 years); focused on NAS; incorporated an experimental (breastfeeding) and control (non-breastfeeding) group, with the definition of *breastfeeding* as initiated and continued as a predominant form of oral feeding; and reported variables included at least one of the following: severity of NAS symptoms, initiation of pharmacological management, duration of pharmacological treatment, and/or LOS.

### Search Strategy and Resources

In December 2020, PubMed, Scopus, Embase, and the Cochrane Library databases were searched for comparative studies of breastfeeding and nonbreastfeeding infants with NAS published between 2006 and 2020 (15 years). The following search terms and combinations were used: prenatal opioid exposure or neonatal opioid withdrawal or neonatal opioid withdrawal syndrome or neonatal substance withdrawal or NAS, breastfeeding, breastfeed. Supplemental Digital Content Table 1 (<http://links.lww.com/NRES/A407>) presents the details of the PubMed and Scopus searches as examples of our search approach. Only studies published in English were included. Hand searches produced no additional "gray" literature or unpublished papers.

### Study Selection

Our selection process began with a review of study abstracts. Full articles were read when necessary before deciding to include or exclude them. Based on our inclusion criteria, four team members (L. C., J. O., J. M. M., and K. M. B.) independently evaluated each abstract/full article. Disagreements were resolved by discussion and consensus. When necessary, we attempted to contact study authors to obtain raw data and/or to confirm the study design details. The study was excluded from this meta-analysis if these data were unavailable or authors could not be reached.

Once studies were selected for inclusion, we conducted a full review and extracted the following data points: author, publication year, country of study origin, study design, number of participants, intervention comparison, outcome evaluated,

**TABLE 1. Existing Published Reviews Related to Neonatal Abstinence Syndrome and Breastfeeding Effects**

<b>Authors (year)</b>	<b>Country of origin</b>	<b>Review type</b>	<b>Inclusion years</b>	<b>Purpose of review</b>	<b>Major outcomes explored</b>	<b>Results</b>	<b>Comments and concerns</b>
Pritham (2013)	USA	Review (type not identified)	1990–2013	Focus: Provision of BF Explore whether provision of BF, SSC, and/or swaddling reduces symptoms, decrease LOS, and decrease pharmacological Tx	<ul style="list-style-type: none"> <li>• BF management of NAS.</li> </ul>	<ul style="list-style-type: none"> <li>• Number of studies included not specified</li> <li>• BF decreases NAS symptoms</li> <li>• Maternal contact during BF also important to decreasing symptoms.</li> <li>• Interventions supporting BF include SSC, swaddling, and rooming-in</li> </ul>	<ul style="list-style-type: none"> <li>• Included overview of existing national standards and guidelines for use of BF with NAS infants</li> <li>• Lacked use of PRISMA</li> </ul>
Cirillo et al. (2016)	USA	Evidence-based brief	2006–2016	Focus: Provision of HM Explore whether provision of HM reduces symptoms, decreases LOS, and decreases pharmacological Tx	<ul style="list-style-type: none"> <li>• Symptom severity</li> <li>• Pharmacological Tx</li> <li>• LOS</li> </ul>	<ul style="list-style-type: none"> <li>• 10 studies included</li> <li>• HM may be beneficial for decreasing               <ul style="list-style-type: none"> <li>○ Severity of NAS</li> <li>○ Pharmacological Tx</li> <li>○ LOS</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Included studies were mostly retrospective chart reviews with small samples</li> <li>• Systematic search; lacked use of PRISMA</li> </ul>
Holmes et al. (2017)	USA	Review (type not identified)	Years not identified (first study 2006)	Focus: Need for pharmacological Tx Considerations for decision-making to inform BF guidelines in coordination when mother is receiving methadone and/or buprenorphine	<ul style="list-style-type: none"> <li>• Effects of methadone and/or buprenorphine on infant BF outcomes including LOS</li> </ul>	<ul style="list-style-type: none"> <li>• 10 studies included</li> <li>• Conclusions were related to balancing pharmacological Tx with BF recommendations</li> </ul>	<ul style="list-style-type: none"> <li>• Purpose of review poorly stated</li> <li>• Results used to support ABM breastfeeding guidelines</li> <li>• Systematic search; lacked use of PRISMA</li> </ul>
Wu & Carre (2018)	USA	Review (type not identified)	1997–2018	Focus: Provision of BF Outcomes in BF vs. formula-fed infants Experimental/ quasi-experimental studies	<ul style="list-style-type: none"> <li>• Symptom severity</li> <li>• Pharmacological Tx</li> <li>• LOS</li> </ul>	<ul style="list-style-type: none"> <li>• 7 retrospective studies included</li> <li>• Collectively, strong correlation between BF               <ul style="list-style-type: none"> <li>○ Reduced LOS</li> <li>○ Decreased symptom severity</li> <li>○ Decreased pharmacological Tx</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Systematic search; lacked use of PRISMA</li> </ul>
Clark (2019)	USA	Policy and practice review	2013–2018	Focus: BF policies and barriers to implementation Examine current BF policies and opioid management, and barriers to policy implementation	<ul style="list-style-type: none"> <li>• Existing policy statements</li> <li>• Barriers exist for policy implementation</li> </ul>	<ul style="list-style-type: none"> <li>• 8 policy statements and 17 original research studies included</li> <li>• All policy statements support BF</li> <li>• Despite policies rates of BF remain low; practice lags behind policy</li> </ul>	<ul style="list-style-type: none"> <li>• Systematic search</li> <li>• Many barriers exist</li> <li>• Healthcare providers are a barrier</li> </ul>
MacVicar & Kelly (2019)	UK	Systematic review	2007–2018	Focus: Nonpharmacological management Explored nonpharmacological management of infants at risk for NAS after prenatal exposure Quantitative and qualitative data included thematic analysis	<ul style="list-style-type: none"> <li>• Consolation therapy</li> <li>• Mother/infant rooming-in</li> </ul>	<ul style="list-style-type: none"> <li>• 14 studies included               <ul style="list-style-type: none"> <li>○ 9 were quality improvement projects</li> </ul> </li> <li>• Most included studies were from USA or Canada</li> <li>• Nonpharmacological Tx reduced need for pharmacotherapy and decreased LOS</li> </ul>	<ul style="list-style-type: none"> <li>• BF not primary focus; later identified</li> <li>• Barriers included               <ul style="list-style-type: none"> <li>○ Reliability of assessment tools,</li> <li>○ Practitioner attitudes</li> <li>○ Limited BF promotion.</li> </ul> </li> <li>• Systematic search; PRISMA guided review</li> </ul>
McQueen et al. (2019)	Canada/USA	Systematic review	1990–2018	Focus: Provision of BF Studies were of quantitative design and included comparison of breastfed and formula-fed newborns with NAS	<ul style="list-style-type: none"> <li>• Symptom severity</li> <li>• Pharmacological Tx</li> <li>• LOS</li> </ul>	<ul style="list-style-type: none"> <li>• 8 studies included</li> <li>• Strong correlation between BF               <ul style="list-style-type: none"> <li>○ Reduced LOS</li> <li>○ Decreased symptom severity</li> <li>○ Decreased pharmacological Tx</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Systematic search; PRISMA guided review</li> <li>• Tx barriers included               <ul style="list-style-type: none"> <li>○ Practitioner attitudes</li> <li>○ Limited BF promotion.</li> </ul> </li> </ul>

*(continues)*

**TABLE 1. Existing Published Reviews Related to Neonatal Abstinence Syndrome and Breastfeeding Effects, Continued**

Authors (year) Country of origin Review type Inclusion years	Purpose of review	Major outcomes explored	Results	Comments and concerns
Ryan et al. (2019) Canada Review (type not identified) 2000–2017	Focus: Nonpharmacological management Explore and summarize the current literature on nonpharmacological Tx of NAS	<ul style="list-style-type: none"> <li>Nonpharmacological management encompasses “environmental control,” “feeding methods,” “soothing techniques,” and “therapeutic modalities”</li> </ul>	<ul style="list-style-type: none"> <li>Number of studies included not specified</li> <li>Effective interventions including: BF swaddling, rooming-in, and SSC</li> <li>Authors recommended a combination of pharmacological Tx, or as stand-alone therapy for less severe NAS cases (Finnegan’s &lt; 8).</li> </ul>	<ul style="list-style-type: none"> <li>Quality of evidence graded using Canadian Task Force on Preventative Health Care guidelines.</li> <li>Systematic search; lacked use of PRISMA</li> </ul>

Note. BF = breastfeeding; SSC = skin-to-skin care; LOS = length of hospital stay; Tx = treatment; NAS = neonatal abstinence syndrome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; HM = human milk; ABM = Academy of Breastfeeding Medicine.

and outcome data (means and standard deviations). Studies that qualitatively fit our inclusion criteria (focused on variables of interest) but did not include the appropriate data for inclusion in our planned meta-analyses are included for commentary and comparison in the Discussion section of this article. For example, we were not able to include studies by Dryden et al. (2012), Lembeck et al. (2020), or Schiff et al. (2018) and their teams because we could not readily extract the needed data for the meta-analysis, such as means and standard deviations (Dryden et al., 2012; Lembeck et al., 2020; Schiff et al., 2018). Instead, these studies were used as comparisons for our discussion to capture these findings as necessary to the overall evidence on breastfeeding and NAS.

### Statistical Methods

We used Review Manager Version 5.3 (The Cochrane Collaboration, 2014) to prepare all analyses, including organization of the characteristics of studies, comparison tables, and study data. Although we assessed heterogeneity using the  $I^2$  statistic, we conducted both fixed- and random-effects analyses per the Cochrane Review standard analytic and reporting guidelines (Higgins et al., 2011). The homogeneity test of included studies was completed using the Mantel-Haenszel test, which selects the corresponding calculation model based on the results of homogeneity testing. There is always the potential for error in statistical analysis. Homogeneity answers the question, “Is the variance found in the meta-analysis due to the effects of the variable of interest rather than sampling error?”

Although we ran both the fixed- and random-effects analyses, we chose to report the random-effects analyses because data were from clinical settings where sampling variability would be expected. Meta-analysis provides more discrete information regarding synthesized magnitude of association between variables of interest and thus increases the potential to answer study questions. A random-effects model was used to pool discontinuous outcomes using risk ratio (RR) and 95%

confidence intervals (CIs). The continuous variables were assessed using the mean difference (MD), and then the combined statistics and 95% CI were calculated. A two-sided  $p$  value of .05 was considered statistically significant.

### Quality Assessment

We used the Cochrane Collaborative Bias Risk Tool to assess the risk of bias in the included clinical trials (Higgins et al., 2011). This tool consists of seven areas: random sequence generation, assignment concealment, blindness of participants and personnel, blinded assessment of results, incomplete results data, selective reporting, and other biases. This tool’s methodological quality is assessed using three levels: low risk of bias, high risk of bias, and unclear risk of bias. Furthermore, we also used the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-1) to evaluate the risk of bias in nonrandomized studies (Sterne et al., 2016). Methodological quality was assessed using three levels: low risk of bias, high risk of bias, and unclear risk of bias. Four authors (L. C., J. O., J. M. M., and K. M. B.) independently assessed quality and resolved any differences through consensus-building discussions.

## RESULTS

### Study Characteristics

Of the 487 articles initially identified, 11 studies (Abdel-Latif et al., 2006; Favara et al., 2019; Isemann et al., 2011; Liu et al., 2015; MacVicar et al., 2018; McDowell et al., 2019; McQueen et al., 2011; O’Connor et al., 2013; Short et al., 2016; Wachman et al., 2013; Welle-Strand et al., 2013), published between 2006 and 2019, qualified for inclusion (nine retrospective cohort studies, one randomized controlled trial, and one mixed cohort study). See the PRISMA diagram (Figure 1) for details. Within the included studies were a total of 6,375 participants, of which 2,529 (40% approximately) were predominately breastfed or received expressed human milk, whereas 3,846 (60%) did not. In none of the studies were infants exclusively breastfed. The qualifying studies were



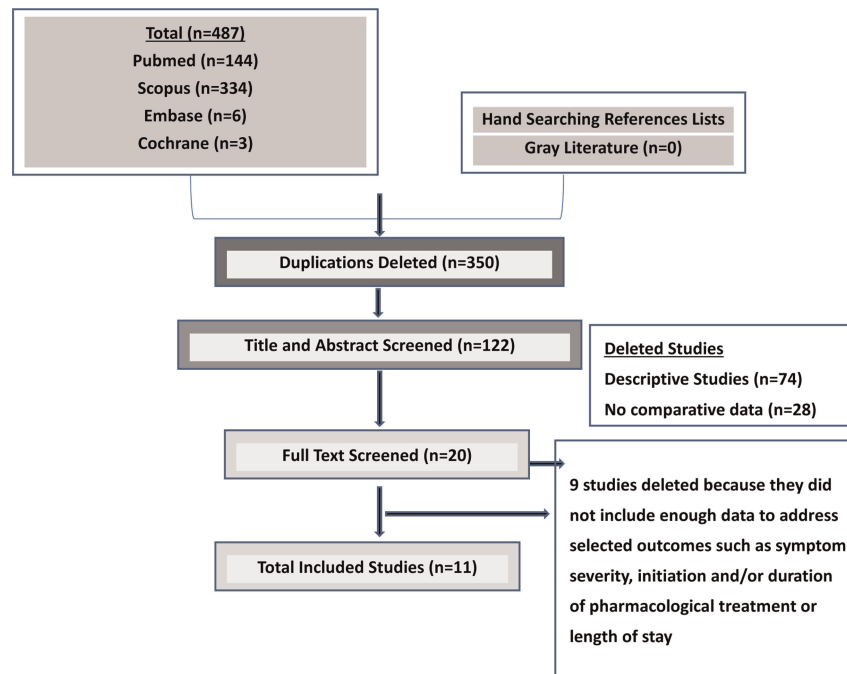


FIGURE 1. Selection process for meta-analysis related to breastfeeding versus nonbreastfeeding for infants with neonatal abstinence syndrome.

conducted in multiple countries, including the United States, Canada, and Europe, yet their characteristics were generally consistent (Table 3).

### Report of Risk of Bias

When reported study findings were unclear, we contacted the authors of the published reports to request additional information or raw data and clarify any aspect of quality assessment not clear from the reports. The Cochrane Collaboration's risk-of-bias tool (Higgins et al., 2011) was used to evaluate the quality of the one randomized clinical trial included in this review (MacVicar et al., 2018). This study was found to have a low overall risk of bias (see Supplemental Digital Content Table 2, <http://links.lww.com/NRES/A408>, for details).

The remaining 10 studies (Abdel-Latif et al., 2006; Favara et al., 2019; Isemann et al., 2011; Liu et al., 2015; McDowell et al., 2019; McQueen et al., 2011; O'Connor et al., 2013; Short et al., 2016; Wachman et al., 2013; Welle-Strand et al., 2013) were assessed using the ROBINS-1 (Sterne et al., 2016; see Supplemental Digital Content Table 3, <http://links.lww.com/NRES/A409>). Of these 10 studies, nine used retrospective cohort designs (Abdel-Latif et al., 2006; Favara et al., 2019; Isemann et al., 2011; Liu et al., 2015; McDowell et al., 2019; McQueen et al., 2011; O'Connor et al., 2013; Short et al., 2016; Wachman et al., 2013), and one used a mixed retrospective and prospective cohort design (Welle-Strand et al., 2013; see Table 2).

All 11 studies included in this meta-analysis were found to have a low to moderate overall risk of bias. Overall, the study's results were objective (i.e., the proportion of pharmacological

treatment and LOS). Risks were also low to moderate because most studies were of retrospective designs, and thus, selection bias was low; however, the degree of missing or interpellated data was seldom reported. In addition, the definition of breastfeeding across these studies was liberal, and for the most part, researchers did not use well-known standardized definitions of breastfeeding; though, most did identify how they defined breastfeeding within their studies (see Table 2).

### Meta-Analysis Results for Each Variable

In compliance with the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.0), we performed both the fixed-effects model and random-effects model to analyze the data. The outcomes were relatively the same for both models. However, because these data were collected in the clinical setting, the randomized effect analyses are reported for each of the four variables of interest.

**Severity of Symptoms** Three retrospective cohort studies evaluated the effects of breastfeeding on the severity of NAS symptoms using mean Finnegan scores (Liu et al., 2015; McQueen et al., 2011) and mean peak scores (O'Connor et al., 2013) and observed that infants exclusively breastfeeding had a lower Finnegan score relative to nonbreastfeeding newborns (see Table 3). There was no significant homogeneity among the included studies ( $I^2 = 0\%$ ), and thus, any variance in the findings across the included studies could not be attributed to the variable of interest.

McQueen et al. (2011) compared the Finnegan scores of breastfeeding versus formula-fed newborns to determine if

**TABLE 2. Included Study Characteristics and Findings by Primary Outcome Investigated**

<b>Authors (year) Country</b>	<b>Study design breastfeeding definition</b>	<b>Total participants Intervention vs. comparison</b>	<b>Outcomes investigated</b>	<b>Reported findings Breastfeeding vs. nonbreastfeeding</b>
<b>Severity of NAS symptoms—Major outcome</b>				
Liu et al. (2015) Australia Data from 2000–2006	<u>Retrospective cohort study</u> Predominant milk type consumed on second day of life. Infants with >50% breastfeeding or expressed human milk were in the breastfeeding group.	<u>182 total participants</u> 32 infants BF 150 infants No-BF Data compared between groups	Severity of symptoms	5.1(1.3) vs. 5.4(1.1) $p > .05$ *Clinical significance
McQueen et al. (2011) Canada Data from 2007–2008	<u>Retrospective cohort study</u> Infants breastfed >75% of all feedings were breastfed group. Infants breastfed >75% and <25% were combination-fed group. Infants breastfed >25% or formula fed were formula-fed group. Breastfeeding or expressed human milk were in the breastfeeding group.	<u>28 total participants</u> 8 predominately BF 11 combination fed 9 predominately formula Data compared between groups	Severity of symptoms	4.9 (2.9) vs. 6.9(4.2) $p = .0074$ 4.9(2.9) vs. 6.5(3.7) $p = .0074$ # NAS scores recorded across feeding types $p = .001$ , magnitude of scores (severity) $p = .0001$ and area score $p = .04$ by infant feeding method
O'Connor et al. (2013) USA Data from 2007–2012	<u>Retrospective cohort study</u> Any amount of BF at birth and 6–8 weeks postpartum were classified as BF at respective time interval, even if infants also received formula.	<u>85 total participants</u> 65 infants BF 20 infants No-BF Data compared between groups Data from an intensive maternal–infant opioid dependence treatment program where BF was highly encouraged	Severity of symptoms Tx Initiated LOS Other	Finnegan's scores 8.83(3.56) vs. 9.65(2.58) $p = .17$ Infants Tx NAS, $n$ (%) BF = 23.1% No-BF = 30% $p = .56$ LOS 7.08(4.39) vs. 6.60(1.70) $p > .05$ 66% of infants receiving BF in hospital were BF at 6–8 weeks *Clinical significance
<b>Initiation of pharmacological treatment—Major outcome (some included studies noted above)</b>				
Abdel-Latif et al. (2006) Australia Data from 1998–2004	<u>Retrospective cohort study</u> Predominant milk type consumed on 5th day of life. Those with >2 feeds per day of formula were “formula” group, whereas others were “breastfeeding” group.	<u>190 total participants</u> 85 infants BF 105 infants No-BF Data compared between groups	Tx initiation Tx duration LOS	52.9% vs. 79% BF CI (0.353) 0.356 No BF (0.178–0.711) $p = .003$ *4.8(0.14) vs. 5.7(0.18) $p > .05$ *14.7(14.9) days vs. 19.5 (15.0) days $p = .049$
McDowell et al. (2019) USA Data from 2015–2018	<u>Retrospective cohort study</u> No definition of BF provided	<u>271 total participants</u> 133 infants BF 138 infants No-BF Data compared between groups	Tx initiation Tx duration LOS	52% vs. 57% $p = .46$ 12 days vs. 11 days $p = .67$ 11 days vs. 14 days $p = .08$ *Clinical significance
Wachman et al. (2013) USA Data from 2011–2012	<u>Prospective multicenter cohort study</u> BF outcomes were an incidental finding not study purpose. No definition of BF provided	<u>86 total participants</u> 38 neonates BF 48 neonates No-BF	Tx initiation LOS	50% vs. 77% $p = .009$ 15.8 days (11.5–20.1) vs. 27.4 days (22.5–32.3) $p < .001$
Welle-Strand et al. (2013) Norway Data from 1999–2009	<u>Retrospective cohort study</u> 1999–2004 retrospective data 2005–2007 prospective data 2007–2009 retrospective data No definition of BF provided	<u>124 total participants</u> 95 infants BF 29 infants No-BF Data compared between groups	Tx initiation Tx duration	Methadone group Treated for NAS, 53% vs. 80% Tx duration, days mean $\pm$ SD (range) 28.6 $\pm$ 19.1 (1–90) 46.7 $\pm$ 26.3 (17–122) $p < .05$
<b>Duration of pharmacological treatment—Major outcome (some included studies noted above)</b>				
Favara et al. (2019) USA Data from 2010–2016	<u>Retrospective cohort study</u> Not all eligible infants in study sites were captured in data. Any BM and exclusive BM were grouped together b/c no difference for outcomes found between those groups.	<u>1,738 total participants</u> 70 infants BF 430 infants BF/formula 1,308 infants No-BF Data compared between groups	Tx duration LOS	Days, median (IQR) 14 (9–22) 17 (10–26) $p = .04$ Days, median (IQR), 19 (13–28) 20 (13–31) $p = .01$

(continues)

TABLE 2. Included Study Characteristics and Findings by Primary Outcome Investigated, Continued

Authors (year) Country	Study design breastfeeding definition	Total participants Intervention vs. comparison	Outcomes investigated	Reported findings Breastfeeding vs. nonbreastfeeding
LOS—Major outcome (some included studies noted above)				
Isemann et al. (2011) USA Data from 2002–2007	Retrospective cohort study No definition of BF provided	122 total participants 56 infants BF 66 infants No-BF Data compared between groups	Tx duration  LOS	Findings reported in figure, but not reported in text $p < .04$ *NOT used in our analysis Median 12.5 (3–51) vs. 18.5 (9–43) days $p = .01$
MacVicar et al. (2018) Scotland Data from 2014–2015	Randomized controlled trial Prospective mixed-methods feasibility study Breastfeeding liberally defined as feeding at breast, ongoing attempts to latch onto breast, and expressed breastmilk given for >50% of oral intake. Qualitative data—Maternal experience of healthcare practices, attitudes, and postnatal environment influenced their perceptions of breastfeeding support.	14 total participants 11 infants BF 3 infants No-BF Data compared between groups Standard baby-friendly initiative care vs. additional support including dedicated BF support, personalized capacity-building approach, and a low-stimuli environment for 5 days	LOS	10.8(6.7) days vs. 30.0(11.8) days $p > .05$ *Clinical significance
Short et al. (2016) USA Data from 2012–2014	Retrospective cohort study No definition of BF provided Yes/no BF at discharge	3465 total participants 1,576 infants BF 1,968 infants No-BF Data compared between groups	LOS	Median LOS 10 days (5–19) vs. 12 days (5–22) $p = .008$ *Clinical significance

Note. Means and standard deviations (SD) are noted in the reported findings. NAS = neonatal abstinence syndrome; BF = breastfeeding; No-BF = nonbreastfeeding; Tx = treatment; LOS = length of hospital stay; BM = breastmilk; \*Clinical significance = author reported; findings are meaningful for patient care and clinical outcomes.

the feeding method affected symptom severity (McQueen et al., 2011). Their statistically significant results demonstrated that breastfeeding infants required less monitoring and had a lower Finnegan score than formula-fed infants. The other two studies showed clinical significance (i.e., findings are meaningful for patient care and clinical outcomes, as reported by the author) without statistically significant differences between groups (Liu et al., 2015; O'Connor et al., 2013). Overall, our meta-analysis results indicate no significant differences between groups for breastfeeding efficacy for decreasing severity of NAS symptoms (RR =  $-0.27$ , 95% CI [ $-0.56$ ,  $0.02$ ],  $p = .07$ ).

**Initiation of Pharmacological Treatment** Five studies (Abdel-Latif et al., 2006; McDowell et al., 2019; O'Connor et al., 2013; Wachman et al., 2013; Welle-Strand et al., 2013) found that breastfeeding was associated with a lower proportion of infants requiring initiation of pharmacological treatment compared with nonbreastfeeding infants (see Table 4). Of these five studies, four were retrospective cohort designs (Abdel-Latif et al., 2006; McDowell et al., 2019; O'Connor et al., 2013; Wachman et al., 2013), and one used a prospective cohort design (Welle-Strand et al., 2013). There was significant heterogeneity among the included studies ( $I^2 = 26\%$ ). Two studies demonstrated clinical significance with no statistically significant difference between groups within the individual studies (Abdel-Latif et al., 2006; Wachman et al., 2013).

The remaining three studies observed a statistically significant difference associated with improved outcomes (no

need for initiation of pharmacological treatment for the breastfeeding infants vs. the nonbreastfeeding infants; McDowell et al., 2019; O'Connor et al., 2013; Welle-Strand et al., 2013). Welle-Strand et al. (2013) conducted the only prospective study to date examining breastfeeding effects on the need for pharmacological treatment (initiation) with a sample of 124 participating infants with NAS (95 breastfeeding infants vs. 29 matched nonbreastfeeding), which demonstrated significantly positive findings (Welle-Strand et al., 2013). Meta-analysis results indicate a significant difference between groups for the efficacy of breastfeeding in decreasing the need for initiation of pharmacological treatment (RR =  $0.77$ , 95% CI [ $0.66$ ,  $0.90$ ],  $p = .001$ ).

**Duration of Pharmacological Treatment** Three studies examined breastfeeding effects on duration of pharmacological treatment (Abdel-Latif et al., 2006; Favara et al., 2019; Welle-Strand et al., 2013); two studies (Abdel-Latif et al., 2006; Welle-Strand et al., 2013) used a retrospective cohort design, and the third (Favara et al., 2019) used a prospective cohort design. Both Favara et al. (2019) and Welle-Strand et al. (2013) found that duration of pharmacological treatment was significantly shorter for infants with NAS who were breastfeeding or received expressed human milk, compared to infants who were not breastfed (Favara et al., 2019; Welle-Strand et al., 2013). In the study conducted by Abdel-Latif et al. (2006), differences in the duration of pharmacological treatment did not reach statistical significance; however, the authors noted clinical significance

**TABLE 3. Comparisons Across Studies for Breastfeeding Versus Nonbreastfeeding Infants**

Study or subgroup	Breastfeeding			Nonbreastfeeding				Std. mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI
Severity of NAS symptoms								
Liu et al. (2015)	5.1	1.3	32	5.4	1.1	150	57.1%	-0.26 [-0.65, 0.12]
McQueen et al. (2011)	4.9	2.9	8	6.9	4.2	11	9.7%	-0.51 [-1.44, 0.42]
O'Connor et al. (2013)	8.83	3.56	65	9.56	2.58	20	33.2%	-0.22 [-0.72, 0.29]
Total (95% CI)			105			181	100.0%	-0.27 [-0.56, 0.02]
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.31, df = 2 (p = .86); I <sup>2</sup> = 0% Test for overall effect: Z = 1.84 (p = .07)								
Duration of pharmacological treatment for NAS								
Abdel-Latif et al. (2006)	85.4	71.7	85	108.2	81.8	105	31.2%	-0.29 [-0.58, -0.01]
Favara et al. (2019)	15.5	6.5	430	18	8	1308	48.1%	-0.33 [-0.44, -0.22]
Welle-Strand et al. (2013)	28.6	19.1	95	46.7	26.7	29	20.7%	-0.85 [-1.28, -0.42]
Total (95% CI)			610			1442	100.0%	-0.43 [-0.68, -0.17]
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 5.60, df = 2 (p = .06); I <sup>2</sup> = 64% Test for overall effect: Z = 3.32 (p = .0009)								
Length of hospital stay for infants with NAS								
Abdel-Latif et al. (2006)	14.7	14.9	85	19.5	15	105	17.1%	-0.32 [-0.61, -0.03]
Favara et al. (2019)	20.5	7.5	430	22	9	1308	20.1%	-0.17 [-0.28, -0.06]
Isemann et al. (2011)	27	24	56	29	20	66	15.7%	-0.09 [-0.45, 0.27]
MacVicar et al. (2018)	10.8	6.7	11	30	11.8	3	2.7%	-2.31 [-3.94, -0.68]
O'Connor et al. (2013)	7.08	4.39	65	6.6	1.7	20	12.6%	0.12 [-0.38, 0.62]
Short et al. (2016)	12	7	1576	13.5	8.5	1968	20.5%	-0.19 [-0.26, -0.12]
Wachman et al. (2013)	15.8	4.3	38	27.4	4.9	48	11.3%	-2.47 [-3.04, -1.91]
Total (95% CI)			2261			3518	100.0%	-0.47 [-0.75, -0.18]
Heterogeneity: Tau <sup>2</sup> = 0.10; Chi <sup>2</sup> = 70.54, df = 6 (p < .00001); I <sup>2</sup> = 91% Test for overall effect: Z = 3.23 (p = .001)								

Note. SD = standard deviation; IV = inverse variance; NAS = neonatal abstinence syndrome; CI = confidence interval.

(see Table 3; Abdel-Latif et al., 2006). It is important to note that there was significant heterogeneity among the included studies (I<sup>2</sup> = 64%). Overall, meta-analysis results indicate significant differences between groups, with decreased duration of pharmacological treatment for breastfed infants with NAS (MD = -0.43, 95% CI [-0.68, -0.17], p = .0009).

**LOS** Five studies (Abdel-Latif et al., 2006; Favara et al., 2019; Isemann et al., 2011; MacVicar et al., 2018; Short et al., 2016) found that LOS was significantly shorter for infants with NAS who were exclusively breastfeeding, compared with those who were not (see Table 3). Nevertheless, there was again significant heterogeneity among the included studies (I<sup>2</sup> = 91%),

**TABLE 4. Need for Initiation of Pharmacological Treatment for Breastfeeding Versus Nonbreastfeeding Infants With Neonatal Abstinence Syndrome**

Study or subgroup	Breastfeeding		Nonbreastfeeding			Risk ratio
	Events	Total	Events	Total	Weight	M-H, random, 95% CI
Abdel-Latif et al. (2006)	45	85	83	105	30.1%	0.67 [0.54, 0.84]
McDowell et al. (2019)	69	133	77	138	30.5%	0.93 [0.75, 1.16]
O'Connor et al. (2013)	15	65	6	20	3.6%	0.77 [0.34, 1.72]
Wachman et al. (2013)	19	38	37	48	15.7%	0.65 [0.46, 0.92]
Welle-Strand et al. (2013)	54	95	20	29	20.1%	0.82 [0.61, 1.11]
Total (95% CI)		416		340	100.0%	0.77 [0.66, 0.90]
Total events	202		223			
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 5.39, df = 4 (p = .25); I <sup>2</sup> = 26% Test for overall effect: Z = 3.25 (p = .001)						

Note. CI = confidence interval.



precluding a higher level of specificity in developing the model. Although only two of the five studies individually demonstrated statistical significance (Favara et al., 2019; Isemann et al., 2011), overall, the meta-analysis results indicate significant differences between groups in efficacy of breastfeeding for decreasing LOS (MD = -0.47, 95% CI [-0.75, -0.18],  $p = .001$ ).

## DISCUSSION

The findings of our meta-analysis indicate that breastfeeding is associated with decreased need for initiation and duration of pharmacological treatment and shorter LOS for infants with NAS. However, we did not find a significant effect on breastfeeding and severity of symptoms. This could be related to the variability in Finnegan scoring across studies and how scores are used to make treatment decisions. With a recommended scoring frequency of every 2–4 hours, most treatment protocols suggest that three consecutive scores of 8 or two successive scores of 12 or higher warrant the initiation of pharmacotherapy (Devlin et al., 2020). However, two studies reported slight variations in the assessment protocol (McQueen et al., 2011; O'Connor et al., 2013). One study did not report specific information related to NAS scoring assessment (Liu et al., 2015). The heterogeneity (variability) in study characteristics precluded more quantitative analyses that are concise. Although our findings are significant for these three variables of interest, we acknowledge the need for further research with stronger study designs.

In addition, because of variable reporting, we were unable to make any formal conclusions about the function of breastfeeding in light of other relevant secondary outcomes such as discrete symptoms of NAS or type of pharmacological treatment (Abdel-Latif et al., 2006; O'Connor et al., 2013; Welle-Strand et al., 2013), use of mother–infant skin-to-skin contact (O'Connor et al., 2013), and/or greater chances of parental involvement (Abdel-Latif et al., 2006). Even with these limitations, breastfeeding appears to be a viable approach to managing NAS. Because many of the studies that met our inclusion criteria used retrospective cohorts, it is crucial to consider the findings in light of implications for causality and variability in trends in current standards of care for infants with NAS, which may not be reflected in these results.

As breastfeeding is becoming more widely implemented as an intervention for NAS, the existing literature is growing. As such, this meta-analysis builds on our understanding of the role of breastfeeding in the care of infants with NAS, providing researchers and clinicians the ability to evaluate the strengths and weaknesses of the literature in this focused area. Nonetheless, breastfeeding is not implemented in isolation. In the included studies, many encountered co-interventions, including changes in Finnegan scoring practices that may explain some of the observed improvement in outcomes (McQueen et al., 2011). Although the results of all included studies could be considered biased by factors that reduce symptoms of NAS,

such as introduction or choice of pharmacological treatment (Abdel-Latif et al., 2006; O'Connor et al., 2013; Welle-Strand et al., 2013), encouraging skin-to-skin contact (O'Connor et al., 2013), and greater chances of parental involvement (Abdel-Latif et al., 2006), we believe that these covariates are not confounding factors but mediating factors for the benefits of increasing breastfeeding.

Historically, pharmacological treatment has been the cornerstone of care for infants with NAS (Jansson & Patrick, 2019; Jansson et al., 2016; Patrick et al., 2016; Ryan et al., 2019). Pharmacological treatment can improve short-term withdrawal symptoms, but this short-term improvement may be at the expense of worsening interim results (such as prolonged LOS). The effect of pharmacological therapy on long-term prognosis is unknown. However, with a diagnosis of NAS, infants are at greater risk for poorer developmental outcomes (Arter et al., 2021), which may be further accentuated by longer LOS and separation from primary caregivers.

Therefore, nonpharmacological measures, such as rooming-in, skin-to-skin holding, acupuncture, low stimulation environment, and encouraging mothers to breastfeed their infants, may be as or even more critical in providing support for the infant and their family. Although controversial in the past, breastfeeding infants with NAS is now known to convey additional benefits specific to these infants that could outweigh the potential risks (Wu & Carre, 2018). Studies measuring the effect of other nonpharmacological therapies in combination with breastfeeding for infants with NAS are warranted. Furthermore, exploring the associations between exclusive breastfeeding and any breastfeeding relative to no breastfeeding is also of interest.

Although breastfeeding has the potential to improve outcomes for infants with NAS, several studies (Clark, 2019; Maguire et al., 2015, 2018; McGlothen-Bell et al., 2020) confirm the challenges and barriers to breastfeeding that mother–infant dyads affected by NAS may experience. Infants with NAS may be at increased risk for feeding difficulties, which has the potential to preclude progression of successful oral feeding (Maguire et al., 2018). Symptoms of withdrawal, such as fussiness and increased irritability, can increase difficulty with coordination of the suck-swallow-breathe reflex necessary for oral feeding (McGlothen-Bell et al., 2020). This irritability may also make interpretation of feeding cues difficult, further compromising breastfeeding success (Maguire et al., 2015). Future research could assess behavioral feeding cues specific to infants with NAS.

Furthermore, mothers of infants with NAS face unique barriers to breastfeeding, including guilt and misinformation on the safety of breastfeeding as well as attitudes of health professionals while receiving MAT (Clark, 2019; Demirci et al., 2015; McGlothen et al., 2018; Schiff et al., 2018). Mothers are also challenged by lack of social support and issues related to social determinants of health, including economic instability, discrimination, and access to safe housing (Maguire et al.,

2015). Little empirical evidence currently exists regarding population-specific strategies or individualized interventions to increase breastfeeding success for mother–infant dyads affected by NAS. As such, further investigation of targeted interventions used to increase breastfeeding among this population is warranted. For example, peer-to-peer, lactation-based support has been suggested as a viable option to encourage breastfeeding in mothers with opioid use disorder (Demirci et al., 2015; McGlothen et al., 2018).

Although findings from this study suggest the importance of breastfeeding for infants with NAS, more research is needed to understand the underlying mechanisms by which human milk improves outcomes related to NAS. As such, the composition of human milk in this population deserves further investigation. In addition, biological mediators should be explored to develop and support improved breastfeeding practices and promote long-term infant development. One retrospective cohort study evaluated opioid-dependent mother–infant pairs and observed that human milk could improve NAS symptoms regardless of infant gestational age and type of substance exposure (Abdel-Latif et al., 2006). The primary outcomes included decreased LOS and the need for pharmacological treatment. Another retrospective study (Dryden et al., 2012) assessed the relationship between breastfeeding and the need for pharmacological treatment in infants with NAS. The authors of this study found that infants with prenatal opioid exposure who were breastfed for  $\geq 72$  hours in hospitals were less likely to require medication. These are significant findings to guide practice recommendations.

Furthermore, our meta-analysis demonstrates several strengths, including strict adherence to the Cochrane Library for systematic review and meta-analysis for data analysis plan and mitigating risk of bias using risk assessment tools (Higgins et al., 2011). We also used a comprehensive search strategy, including multiple electronic databases and additional strategies for finding and including all available studies. To our knowledge, this is the first meta-analysis to evaluate whether breastfeeding results in improved outcomes for infants with NAS. Combining all relevant evidence, including data from a recent *randomized controlled trial*, within a meta-analysis, provided a quantitative synthesis of these data, which adds to the existing science.

Several limitations need to be considered when considering the results of this meta-analysis. Breastfeeding was not well defined nor universally defined across the studies. We combined studies where breastfeeding was predominant for feeding modes. The most universally accepted definitions of breastfeeding were not used within any of the included studies. Historically, the term *breastfeeding* has been indicative of feeding an infant at the breast of their mother. Though, the term has become more ambiguous with the introduction of various feeding methods, including the use of high-efficiency breast pumps and cup and bottle-feeding (Rasmussen et al., 2017). As such,

measures of breastfeeding remain inconsistent, highlighted in our review of the literature. Previous literature has proposed developing and utilizing a comprehensive set of terms related to breastfeeding (Rasmussen et al., 2017).

Table 2 provides the definition of breastfeeding defined within each of the included studies. We believe these definitions are similar enough to complete our analysis, yet we acknowledge the differences in meaning limit our results. In addition, none of the included studies involved a group of infants who were exclusively breastfed, where the results could have been more supportive of this intervention. Only one study had an exclusively breastfed group of infants with NAS (Schiff et al., 2018); that study was not included in the meta-analysis because we could not extract the needed data to complete the analysis. This omission of exclusive breastfeeding also limits recommendations we can assert from our results. Although most of the studies used regression models to examine outcomes, seldom did the researchers adjust for covariates in their individual findings, which also adds to the limitations of our results.

Although efforts were taken to identify and mitigate risk for bias, this meta-analysis could be limited by publication bias. For example, studies with positive findings are often more likely to be accepted for publication. In addition, to fully identify conflicting or significant outcomes, we did include studies, regardless of whether breastfeeding was the primary target of the intervention. Thus, the included studies lack sufficient capacity to assess all four of the outcomes we thoroughly investigated.

Other limitations that must be acknowledged include the fact that this meta-analysis only included one randomized clinical trial (MacVicar et al., 2018) with a small sample and one prospective cohort study (Welle-Strand et al., 2013) with a moderate sample size. Therefore, publication bias and meta-regression were not assessed or completed across all the studies. For our meta-analysis, studies were included only if data were reported with the appropriate data, such as means and standard deviations about the variables of interest. For instance, several studies (Dryden et al., 2012; Lembeck et al., 2020; Schiff et al., 2018) reported that our variables of interest were not included as we could not extract the needed statistical data. Finally, all the included studies were published in English, resulting in the exclusion of other qualified articles reported in other languages. Even with these limitations, we did find results that could be used to guide practice. More prospective studies with stronger designs are needed before deriving definitive conclusions.

## Conclusion

There is consistent evidence supporting breastfeeding as an effective method for encouraging positive outcomes for infants with NAS concerning initiation and duration of pharmacological treatment and LOS. Our meta-analysis yielded convincing data indicating that breastfeeding is beneficial for newborns

and infants with NAS. All included studies in this review were of low quality, most were retrospective designs, and results were consistent throughout studies. In a high-quality and comprehensive clinical care setting with lactation and family support for mothers, breastfeeding and optimally exclusive breastfeeding are recommended as the preferred feeding method for infants with NAS.











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