

Infant Feeding Method and Neonatal Abstinence Syndrome

Outcomes: A Systematic Review

by

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### Abstract

*Background:* Neonatal Abstinence Syndrome (NAS) is a complex disorder, observed in infants experiencing symptoms of withdrawal, as a result of in utero exposure to the maternal use of opioids. Breastfeeding has been recognized as the optimal source of nutrition for infants. While the advantages associated with breastfeeding are undisputed, the promotion of breastfeeding for infants diagnosed with neonatal abstinence syndrome is inconsistent. There is evidence to suggest that breastfeeding infants who have been exposed to opioids in utero may improve NAS outcomes.

*Aim:* A systematic review was conducted to assess and critically appraise the existing literature regarding the effect of infant feeding method among infants with Neonatal Abstinence Syndrome (NAS) on neonatal outcomes.

*Method:* A systematic search of the literature of feeding methods among infants with NAS was conducted using the electronic databases Pubmed, CINAHL, Nursing and Allied Health, PyschINFO, Evidence Based Medicine, Web of Science, and Medline (EMBASE). Studies were eligible for inclusion in the review if they fulfilled the following criteria: (1) reported original data on outcomes related to infant feeding and NAS, (2) the study method included any type of quantitative design that included an inpatient comparison group of breastfed and formula fed infants with NAS, and (3) the articles were published in English in a peer reviewed journal. All articles selected for inclusion were assessed for methodological quality by first and secondary author using the JBI standardized critical appraisal checklist for cohort/case control studies and the JBI standardized critical appraisal checklist for randomized controlled studies. The principal author extracted the data from the full text studies and entered it into a data extraction template developed for the systematic review. The secondary authors independently reviewed and

compared the extracted data. The data was synthesized narratively due to the diverse study samples and outcomes that were evaluated.

*Results:* The search identified 491 studies, of which 17 provided information related to NAS and infant feeding method. Eight studies met the inclusion and exclusion criteria after further examination of the full-text studies. The majority of studies found that breastfeeding was associated with a reduced need for pharmacologic treatment and a decrease in the duration of pharmacotherapy when compared to formula-fed or combination-fed infants. Breastfeeding, when compared to formula-feeding, was also consistently associated with a shorter hospitalization and a reduced severity of NAS, including lower Finnegan scores. Studies also identified a later time to withdrawal and a delayed onset of NAS associated with breastfed infants when compared to formula-fed infants.

*Conclusions and Relevance:* The studies consistently identified a trend towards improved NAS outcomes for infants who were breastfed when compared to formula or combination-fed. These findings provide evidence for breastfeeding as an effective non-pharmacologic treatment for NAS. Breastfeeding among stabilized mothers on Opioid Maintenance Therapy (OMT) should be recommended as a non-pharmacologic approach to improving NAS outcomes.

## Infant Feeding Method and Neonatal Abstinence Syndrome

### Outcomes: A Systematic Review

Research has demonstrated the substantial advantages for infants, mothers, and the community, from breastfeeding (American Academy of Pediatrics, 2005). Due to the considerable benefits associated with human milk, breastfeeding has been recognized as the optimal source of nutrition for infants (World Health Organization, 2001). These advantages include benefits to infant health, nutrition, immunity, and neurodevelopment, as well as maternal health, and community economic benefits (American Academy of Pediatrics, 2005; Boland, 2005; World Health Organization, 2001). While the advantages associated with breastfeeding are undisputed, the promotion of breastfeeding for infants diagnosed with neonatal abstinence syndrome (NAS) is inconsistent (Jansson, Velez, & Harrow, 2004). Understanding the evidence regarding breastfeeding for infants with NAS is an important consideration for clinicians to promote this method of feeding. As such, the purpose of this systematic review was to assess and critically appraise the existing literature regarding the effect of infant feeding method among infants with NAS on neonatal outcomes. This review method was selected to provide a thorough overview of the current literature and to allow for the inclusion of a variety of methodologies, different scoring tools to measure symptomology, and diverse NAS outcomes.

### **Background**

Neonatal Abstinence Syndrome (NAS) is a complex disorder, observed in infants experiencing symptoms of withdrawal, as a result of in-utero exposure to the maternal use of opioids (Stover & Davis, 2015; Sublett, 2013). Neonatal Abstinence Syndrome is a multisystem condition that presents as hyperirritability of the central nervous system, autonomic dysfunction, and gastrointestinal disturbances (Kocherlakota, 2014; Stover & Davis, 2015). The symptoms of

NAS are characterized, but not limited to vomiting, loose stools, poor feeding, tremors, high-pitched crying, altered sleep-wake cycles, seizures, respiratory distress, and temperature instability (Finnegan, Connaughton, Kron, & Emich, 1975; Kocherlakota, 2014; Sublett, 2013). The manifestation of symptoms varies among infants, and the onset, duration, and severity of NAS depend on a number of factors (Kocherlakota, 2014). Neonatal Abstinence Syndrome may be affected by the substance ingested by the mother, the time of the last dose, in-utero duration of exposure, and maternal and placental metabolism (Hudak & Tan, 2012). The diagnosis of NAS is based on symptoms of neonatal withdrawal, rather than the need for pharmacotherapy (Kraft, Stover, & Davis, 2016). The onset of NAS symptoms is typically observed within the first 24-72 hours (Hudak & Tan, 2012).

One method to assess the severity of NAS symptoms is through the use of scoring tools. Scoring tools are used to objectively evaluate the infant for the severity of NAS symptoms, guide pharmacotherapy, and assist in the structured process of weaning (McQueen & Murphy-Oikonen, 2016). Currently, the Finnegan Neonatal Abstinence Scoring Tool is the most commonly used tool, in either its 1975 original format or the modified short form version (Finnegan et al., 1975; Finnegan, 1986). Other tools have been used to score severity of symptoms and guide pharmacologic treatment of NAS, but the Finnegan Neonatal Abstinence Scoring Tool remains the most comprehensive (Wiles, Isemann, Ward, Vinks, & Akinbi, 2014). Regardless of the tool used, inter-observer reliability is an important consideration, due to the subjectivity of the assessment (Kocherlakota, 2014).

Studies have suggested that the incidence of NAS is on the rise. In the United States, for every 1000 hospital births annually, the diagnosis of infant NAS grew from 1.20 to 3.39 between 2000 and 2009 (Patrick et al., 2012). Correspondingly, there was an increase in maternal use or



dependence on opiates from 1.19 in 2000 to 5.63 in 2009 for every 1000 hospital births per year (Patrick et al., 2012). Western Australia (O'Donnell et al., 2009) and Canada (Davies et al., 2016; Dow et al., 2012) have observed similar increases. The etiology of NAS has also had considerable changes over time. In the last 40 years, the precursor of NAS has shifted from primarily being a result of illicit opiate use, to now being inclusive of opioid replacement therapy (ORT) such as methadone and buprenorphine (Hudak & Tan, 2012; Kieviet, Dolman, & Honig, 2013). The rise in opiate use, coupled with the complication of simultaneous licit and illicit substances has led to NAS becoming increasingly common and complex (Kocherlakota, 2014).

Several adverse outcomes have been associated with NAS. Between 2004 and 2013 the number of infants admitted to NICU in the USA for NAS increased from 7 to 27 admissions for every 1000 hospital births (Tolia et al., 2015). The use of pharmacotherapy as a form of NAS treatment also increased from 74% to 87%, with simultaneous growth in the pharmacological duration of treatment (Tolia et al., 2015). Due to the management of withdrawal symptoms through pharmacologic treatment, admission to the NICU and lengthy hospitalizations are often required (Hudak & Tan, 2012; Wachman et al., 2011). Separation of mother and her infant at a critical time for bonding (Abrahams et al., 2010), and overall decreased rates of breastfeeding (Wachman, Byun, & Phillipp, 2010) in this population are added negative outcomes associated with NAS.

While the needs of each infant are unique, the treatment of infant NAS symptoms often follows an approach based on pharmacological drug treatment, with oral morphine or methadone recommended as a first-line medication to treat withdrawal (McQueen & Murphy-Oikonen, 2016; Wiles et al., 2014). Although pharmacotherapy has been well researched, there is a growing body of evidence regarding the impact of infant feeding method on NAS outcomes.

Furthermore, breastfeeding has been established as compatible for mothers stabilized on ORT with no contraindications (McQueen & Murphy-Oikonen, 2016; O'Connor, Collett, Alto, & Brien, 2013). Research has suggested that methadone concentrations found in human milk are low, and women on stable doses of methadone should be encouraged to breastfeed, regardless of maternal methadone dose (McCarthy & Posey, 2000). Despite this indication, the promotion of breastfeeding for NAS infants is inconsistent and varies across hospitals (Jansson, 2009; Provincial Council for Maternal and Child Health, 2012). This systematic review will assess and critically appraise the existing literature regarding the effect of infant feeding method among infants with NAS on neonatal outcomes.

## **Method**

### **Search Strategy**

The electronic databases Pubmed, CINAHL, Nursing and Allied Health, PsychINFO, Evidence-Based Medicine, Web of Science, and Medline (EMBASE) were searched from 1990 to February 2018. Subject terms used in the search strategy included 'neonatal abstinence syndrome' [MeSH] and one of the following additional terms, breast feeding [MeSH], breastfeed\*, or infant formula [MeSH]. To ensure relevant articles had not been missed, the reference lists of included studies were reviewed for additional articles relevant to the initial search. A forward citation search of included studies was completed July 1<sup>st</sup>, 2018 and yielded no additional articles.

### **Study Selection**

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Figure1) (Moher et al., 2009). Studies were eligible for inclusion in the review if they fulfilled the following criteria: 1) reported original data on outcomes related

to breastfed and formula fed infants with NAS, 2) the study method included any type of quantitative design that included an inpatient comparison group of breastfed and formula fed infants with NAS, and 3) the articles were published in English in a peer reviewed journal. For the purpose of this review, NAS was defined as a postnatal withdrawal syndrome in infants that were exposed to opioids in utero (McQueen & Murphy-Oikonen, 2016). Thus, NAS in infants exclusively from substances other than opioids (e.g., Selective Serotonin Reuptake Inhibitors) were excluded from this review. Additional exclusion criteria included: 1) descriptive studies with no comparison of breastfed and formula fed infants with NAS, 2) review articles and 3) infants who were re-admitted to hospital with NAS after discharge.

The first author entered all studies from the search into the Zotero Reference Manager and removed duplicates. The remaining studies were screened for inclusion based on the title and abstract by both the first (CT) and second author (JM). Remaining full text articles were independently reviewed by all authors and inclusion criteria was discussed until agreement was achieved. Articles that did not meet the inclusion and exclusion criteria were eliminated for further review.

### **Data Extraction**

The principal author extracted the data from the full text studies and entered it into a data extraction template developed for the systematic review. The template included the authors' names, year of publication, country, purpose, definition of feeding method, study design, sample size, infant feeding method, in-utero drug exposure, infant treatment, and NAS outcomes. The second and third authors (JM and KM) independently reviewed and compared the extracted data. All differences were discussed, referring back to the article until an agreement was obtained.



### **Assessment of Methodological Quality**

All articles selected for inclusion were assessed for methodological quality by the first and secondary authors (CT & JM) using the Joanna Briggs Institute (JBI) standardized critical appraisal checklist for cohort/case control studies and the JBI standardized critical appraisal checklist for randomized controlled studies (Joanna Briggs Institute, 2014). Studies were evaluated as having a low, moderate, or high risk of bias based on the selection of participants, measures of NAS outcomes, confounding factors, and follow-up care. CT and JM independently reviewed and compared the assessments, and any disagreements were resolved through discussion with the third author KM until an agreement was obtained. No studies were eliminated based on the critical appraisal.

### **Data Synthesis**

The data was synthesized narratively due to the diverse study samples and outcomes that were evaluated. Outcomes evaluated included requirement for pharmacologic treatment, duration of pharmacology, length of hospital stay, and NAS severity scores and time to withdrawal.

### **Results**

The search identified 491 studies, of which 17 provided information related to NAS outcomes and infant feeding method. Further assessment of the inclusion and exclusion criteria eliminated 9 of the studies due to: descriptive studies/no comparison group (n=1); no NAS outcome data (n=3); NAS included substances other than opioids (n=2); no infant feeding method data (n=2); and conference abstract (n=1). A total of 8 articles met all criteria and are included in the review. See Figure 1 for the PRISMA flow diagram.

### **Study Characteristics**

The characteristics of the eight included studies are provided in Appendix A. All of the studies were published between 2006 and 2018, with population samples from 5 countries including Australia (n=2), Canada (n=1), Norway (n=1), the United States (n=3), and Scotland (n=1). The primary purpose for five of the studies was to evaluate the effect of infant feeding method on NAS outcomes (Abdel-Latif et al., 2006; Lui, Juarez, Nair, & Nanan, 2015; McQueen, Murphy-Oikonen, Gerlach, & Montelpare, 2011; O'Connor et al., 2013; Welle-Strand et al., 2013). The other three studies reported NAS outcomes in relation to infant feeding method, although it was not the primary purpose of the study (Isemann, Meinzen-Derr, & Akinbi, 2010; Jansson et al., 2007; MacVicar, Humphrey, & Forbes-McKay, 2017). Six of the studies were retrospective cohort reviews (Abdel-Latif et al., 2006; Isemann et al., 2010; Lui et al., 2015; McQueen et al., 2011; O'Connor et al., 2013) with one of these studies also including a prospective review (Welle-Strand et al., 2013). One study was a matched design (Jansson et al., 2007), and one study was mixed methods including a randomized control trial (MacVicar et al., 2017).

Sample sizes ranged from 14 to 194 mother-infant dyads. Categorization of infant feeding method was based on self-selected samples. However, the definition of breastfeeding varied between studies and one study did not clearly define the feeding method (Isemann et al., 2010). This is an important consideration, as the feeding method in relation to NAS outcomes is evaluated. The prevalence of breastfeeding ranged from 23% to 79%. It is important to consider the variation in breastfeeding rates may be related to the definition of breastfeeding in select studies, with breastfeeding defined as ongoing attempts to latch onto the breast, infants who received breastmilk at birth and postpartum even if they were also given formula, and self-

reported initiation and continuation of breastfeeding (MacVicar, 2017; O'Connor et al., 2013; Welle-Strand, 2013).

All infants were exposed to opioid maintenance therapy (OMT) in utero, including methadone (n=5), buprenorphine (n=1) and either methadone or buprenorphine (n=2). The primary medications used for pharmacologic treatment of NAS was morphine (n=1), phenobarbital (n=1), either morphine or phenobarbital (n=1), methadone or phenobarbital (n=1), and diluted tincture of opium or morphine (n=1). Three studies did not specify the pharmacologic treatment for NAS (see Appendix A).

The Finnegan or a modified version of the Finnegan Scoring Tool was used in all of the studies to assess symptoms of NAS and to guide pharmacologic treatment. However, the studies differed in their evaluation of requirement for pharmacologic treatment. Three studies initiated pharmacologic treatment following two consecutive Finnegan Scores greater than 8 (Abdel-latif et al., 2006; Isemann et al., 2010; Jansson et al., 2007). Two studies initiated pharmacologic treatment following three consecutive Finnegan Scores greater than 8 (McQueen et al., 2011; O'Connor et al., 2013) and three studies did not report the initiation of pharmacologic treatment in relation to NAS Finnegan Scores (Lui et al., 2015; MacVicar et al., 2017; Welle-Strand et al., 2013). Furthermore, the modifications of the tool and/or the number of items were not specified in the studies. All studies explored one or more NAS outcomes including requirement for pharmacologic treatment, overall duration of pharmacotherapy, hospital length of stay, and NAS severity (see Appendix B).

### **Methodological Quality**

Five studies were identified as a low risk of bias (Abdel-latif et al., 2006; Isemann et al., 2010; Jansson et al., 2007; Lui et al., 2015; MacVicar et al., 2017) and three studies were

identified as a moderate risk of bias (McQueen et al., 2011; O'Connor et al., 2013; Welle-Strand et al., 2013). Infant feeding method was self-selected by mothers. Thus, selection bias was present in six of the seven studies appraised with JBI standardized critical appraisal checklist for cohort/case control studies (Abdel-latif et al., 2006; Isemann et al., 2010; Lui et al., 2015; McQueen et al., 2011; O'Connor et al., 2013; Welle-Strand et al., 2013). In one study, selection bias was not present as the groups were matched with respect to race, parity (primiparous versus multiparous), age within 5 years, and methadone dose within 10mg (Jansson et al., 2007). Selection bias was not present in the randomized control trial study, as a computer-generated process was used for true randomization of participants to groups (MacVicar et al., 2018). The majority of the studies identified criteria for categorization of infant feeding method, which included breastfeeding, expressed breastmilk, combination feeding, and formula feeding. However, the definition and categorization of infant feeding method varied between studies. All studies identified using the Finnegan Scoring Tool or a Modified Finnegan to assess NAS and guide pharmacologic treatment. However, the studies differed in protocols for pharmacological initiation and the validity and reliability of the tool was not indicated in most studies. Thus, measurement bias was probable.

Most studies identified confounding factors, including maternal and infant baseline characteristics (maternal OMT, polydrug use, smoking, parity, birth weight, and gestation) and the majority of studies made adjustments in data analysis to account for the confounding factors measured. Finally, due to the majority of the studies being conducted in hospital, the attrition bias was unlikely, and is an overall strength (see Appendix C and D).

**Infant Feeding Method and NAS Outcome: Pharmacology**

All studies reported NAS outcomes in relation to pharmacology, including the need for pharmacologic treatment and/or the duration of pharmacotherapy for NAS (see Appendix B). Among the studies (n=7) evaluating infants who received pharmacologic treatment, two studies reported breastfed infants were significantly less likely to require pharmacologic treatment compared to formula-fed infants (Abdel-Latif et al., 2006; Welle-Strand et al., 2013). Four studies found that breastfed infants were less likely to require pharmacologic treatment when compared to formula-fed or combination-fed infants; however, the results were not statistically significant (Jansson et al., 2007; MacVicar, 2017; McQueen et al., 2011; O'Connor et al., 2013). One study reported no statistical difference in the incidence of pharmacologic treatment when comparing methods of feeding (Lui et al., 2015), and one study did not evaluate the likelihood of requiring pharmacologic treatment for NAS (Isemann et al., 2010).

Three studies evaluated the duration of pharmacologic treatment. In two of the studies, researchers identified statistically significant differences in the *mean* duration of NAS treatment between groups (Abdel-Latif et al., 2006; Welle-Strand et al., 2013). Overall, Welle-Strand et al. (2013) reported all breastfed infants of women on OMT had a statistically significant shorter *mean* pharmacologic treatment for NAS (28.6 days  $\pm$  19.1) in contrast to formula-fed infants of women in OMT (46.7 days  $\pm$  27.2;  $p = <0.05$ ). Welle-Strand et al. (2013) further identified a statistically significant shorter *mean* pharmacologic treatment for breastfed infants of mothers in MMT (31 days  $\pm$  21.4) when compared to formula-fed infants of women in MMT (48.9 days  $\pm$  27.2;  $p = <0.05$ ). However, no differences in duration were found in the buprenorphine-exposed infants. Although not statistically significant, Abdel-Latif et al. (2006) also found that breastfed infants had a shorter *mean* duration of NAS treatment (85 days  $\pm$  71.7) when compared to



formula-fed infants (108.2 days  $\pm$  81.8;  $p = .185$ ). Similarly, Isemann et al. (2010) reported differences in the *median* duration of pharmacologic treatment for NAS, with breastfed infants having a shorter *median* duration of pharmacotherapy (10.8 days) when compared to formula-fed infants (12.4 days;  $p < .35$ ); however, the results were not reported as statistically significant.

### **Infant Feeding Method and NAS Outcome: Length of Stay**

Length of hospital stay was evaluated in four of the eight studies (see Appendix B). Among infants with NAS, two studies found that breastfed infants had a statistically significantly reduced length of stay in hospital when compared to formula-fed infants (Abdel-Latif et al., 2006; Isemann et al., 2010). A shorter *median* hospital stay was identified for breastfed infants (12.5 days; ranging from 3-51 days) when compared to formula-fed infants (18.5 days; ranging from 9 to 43 days;  $p = 0.01$ ) (Isemann et al., 2010). Similarly, Abdel-Latif et al. (2006) found breastfed infants had a shorter *mean* hospital stay (14.7 days  $\pm$  14.9) when compared to formula-fed infants (19.1 days  $\pm$  15.0;  $p = .049$ ). MacVicar et al. (2017) also found the *mean* hospital stay was shorter for breastfed infants (10.8 days  $\pm$  6.7) when compared to formula-fed infants (30.0 days  $\pm$  11.8), however, the significance of the results was not reported. Although, O'Connor et al. (2013) also evaluated the *mean* hospital stay for breastfed (7.08 days  $\pm$  4.4) and formula-fed infants (6.6 days  $\pm$  1.7;  $p = .35$ ), no conclusions were drawn due to complications unrelated to NAS in the group of breastfed infants.

### **Infant Feeding Method and NAS Outcome: NAS Severity**

Severity of NAS symptoms was evaluated in four of the eight studies (see Appendix B). Of the four studies that evaluated NAS severity, all reported outcomes related to *mean* Finnegan scores between groups (Abdel-Latif et al., 2006; Lui et al., 2015; McQueen et al., 2011; O'Connor et al., 2013). Abdel-Latif et al. (2006) reported *mean* Finnegan scores for the first 9

days of life were lower in breastfed infants when compared to formula-fed infants ( $p < .05$ ). Likewise, McQueen et al. (2011) reported *mean* Finnegan scores were lower in breastfed infants ( $4.9 \pm 2.9$ ) when compared to combination-fed ( $6.5 \pm 3.7$ ) and formula-fed infants ( $6.9 \pm 4.2$ ;  $p = .0001$ ). Correspondingly, the *mean* number of Finnegan scores recorded was also lower in breastfed infants ( $25 \pm 23.5$ ) when compared to combination-fed ( $56.2 \pm 39.1$ ) and formula-fed infants ( $95.9 \pm 34.69$ ;  $p = .001$ ) (McQueen et al., 2011). Alternatively, Lui et al. (2015) found no statistical difference in *mean* NAS scores of breastfed infants ( $5.1 \pm 1.3$ ), expressed breastmilk ( $5.7 \pm 0.9$ ) and formula-fed ( $5.4 \pm 1.1$ ;  $p = 0.47$ ). Although the results were not reported as significant, O'Connor et al. (2013) reported breastfed infants were less likely to score 8 or above on the Finnegan Scoring Tool, as well as less likely to score 12 or above when compared to formula-fed infants. Similarly, McQueen et al. (2011) reported a lower *mean* area of Finnegan scores for breastfed infants ( $7.7 \pm 3.5$ ) compared to combination-fed ( $12.4 \pm 4.2$ ) and formula-fed ( $11.4 \pm 2.9$ ;  $p = .04$ ). While O'Connor (2013) reported lower *mean* Finnegan peak scores and a shorter *mean* Finnegan time to peak for breastfed infants when compared to formula-fed infants, neither of these results were reported as statistically significant.

Time to NAS withdrawal was also evaluated in two of the eight studies (Abdel-Latif et al., 2006; Lui et al., 2015) with longer time to the onset of symptoms among breastfed infants. Breastfeeding during the first 2 days of life was significantly associated with a delayed onset of NAS among infants of MMT mothers ( $p=.04$ ) (Lui et al., 2015). Similarly, the *median* time to withdrawal occurred later in breastfed infants (10 days) when compared to formula-fed infants (3 days;  $p = .001$ ) (Abdel-Latif, 2006). Overall, *mean* Finnegan scores were consistently reported as lower in breastfed infants when compared to formula-fed infants with NAS, which suggests

breastfed infants have a delayed onset or a later time to withdrawal when compared to formula-fed infants.

### **Discussion**

The purpose of this systematic review was to assess and critically appraise the existing literature regarding the effect of infant feeding method among infants with Neonatal Abstinence Syndrome. The studies consistently identified a trend towards improved NAS outcomes for infants who were breastfed. The majority of studies found that breastfeeding was associated with a reduced need for pharmacologic treatment and a decrease in the duration of pharmacotherapy when compared to formula-fed or combination-fed infants. Breastfeeding, when compared to formula-feeding, was also consistently associated with a shorter hospitalization and a reduced severity of NAS, including lower Finnegan scores. Studies also identified a later time to withdrawal and a delayed onset of NAS associated with breastfed infants when compared to formula-fed infants. These findings were consistent regardless of the in utero opioid exposure or infant treatment type. It is important to note that breastfeeding has been shown to promote attachment, and appears to sooth agitated infants (Abdel et al., 2006). Breastfeeding has also been suggested as an intervention for the management of NAS infant symptoms (Jansson et al., 2004) thus, proposing that a mothers' breastmilk may have a weaning effect.

While breastfeeding has been associated with positive outcomes for NAS infants, breastfeeding rates among mothers of infants with NAS are low when compared to the rates of breastfeeding among non-substance users (Pritham, 2013). Researchers have identified a number of challenges that exist for the opioid-dependent mother and her infant. NAS is related to feeding difficulties, including nasal stuffiness, uncoordinated movements, and complications with sucking (Jansson, Velez, & Butz, 2017), which may impact a mother's ability to initiate or

successfully breastfeed. Outcomes related to NAS often lead to a separation of mother and her infant at a critical time for bonding, including an increased risk for admission to the NICU, prolonged hospital stay, and the use of pharmacotherapy (Tolia et al., 2015). These outcomes and the increased likelihood of mother and infant separation may create potential barriers to breastfeeding. Further barriers to breastfeeding in this population include a lack of information or inconsistent promotion of breastfeeding by healthcare professionals (Jansson, 2009; McQueen & Murphy-Oikonen, 2016). Thus, suggesting that despite the benefits of breastfeeding, structural barriers may decrease rates of breastfeeding in this population.

Understanding the influences surrounding a woman's decision to breastfeed is another important consideration. Feelings of guilt and distress may be experienced by many opioid-dependent mothers due to their infant's in utero exposures and NAS symptomology, which may create challenges surrounding a mother's decision to breastfeed (Pritham, 2013; Velez & Jansson, 2008). Some additional factors that contribute to the decision to breastfeed include knowledge of breastfeeding, current physical and mental health, and social influence (Pritham, 2013). Patrick et al. (2012) suggest that the majority of opioid-dependent pregnant women are socioeconomically disadvantaged. Low socioeconomic status along with marital status, age and education also appear to play a role in influencing a mother's decision to breastfeed (Pritham, 2013). Additionally, there is a complexity surrounding the mother-infant dyad, particularly when the mother has a substance use disorder and a sexual abuse history (Jansson, Velez, & Butz, 2017). Survivors of sexual abuse may experience a distorted view of the dual role of their breasts as both sexual and maternal objects, thus contributing to issues surrounding the decision of breastfeeding in this population (Jansson, Velez, & Butz, 2017). Given both the structural and personal barriers to breastfeeding, and the importance of the postnatal period for mother-infant



bonding and attachment (Shannon, Blythe, & Peters, 2016; Tolia et al., 2015), an increased understanding surrounding the evidence of breastfeeding for NAS is crucial for consistent promotion of this method of feeding. The included studies of this systematic review have consistently supported positive outcomes associated with breastfeeding when compared to formula or combination-fed infants.

### **Limitations**

Although breastfeeding was consistently associated with positive NAS outcomes among diverse populations, various methodological weaknesses were evident. Six of the eight included studies relied on the accuracy of medical records through a retrospective design. The other two included studies were a small sample matched design and a mixed methods pilot study, both of which did not evaluate NAS outcomes in relation to feeding method, as the primary purpose. Furthermore, two of the included studies did not identify a clear definition of the categorization of feeding method, which is an important consideration, as the NAS outcomes were compared between feeding modalities. A number of studies had small sample sizes, and the in-utero opioid exposure and postnatal infant treatment varied between studies. While limitations were apparent, the critical appraisal identified that the majority of the included studies ( $n = 5$ ) were a low risk of bias for cohort studies. Despite these limitations, consistent trends were found that suggest that breastfeeding is associated with positive NAS outcomes, including a reduced need and duration of pharmacologic treatment, shorter hospitalization, delayed onset of NAS, and a reduced severity of NAS, including lower Finnegan scores.

### **Implications for Practice**

These findings have important clinical implications and suggest that breastfeeding may be an effective non-pharmacologic intervention in the treatment of infants with NAS. As such,



breastfeeding should be encouraged among mothers on OMT, where no other contraindications for breastfeeding are present (McQueen & Murphy-Oikonen, 2016; Pritham, 2013). It is important to consider that the promotion of breastfeeding in this population is inconsistent (Jansson, Velez, Harrow, 2004). Thus, gaps in knowledge may exist among healthcare providers regarding breastfeeding compatibility, contraindications, and the potential benefits of breastfeeding in this population. Education of healthcare providers may assist in promoting breastfeeding in opioid-dependent mothers when contraindications are not present. Early and consistent maternal education surrounding the benefits of breastfeeding, including the potential to improve NAS outcomes is needed, as this knowledge may increase breastfeeding initiation and duration in this population. In hospital supports and follow-up services may be beneficial to both mother and infant, however further research is necessary to determine effective interventions to support mothers on OMT.

### **Implications for Future Research**

The findings from this systematic review have implications for future research. Larger studies, with a prospective design, are necessary to continue to assess the effect of infant feeding method on NAS outcomes. Future research which compares different OMT in relation to feeding method and NAS outcomes is an important consideration to expand the knowledge surrounding this population. To further understand both the structural and personal barriers to breastfeeding in this population, qualitative research which explores the experiences and perceptions of opioid-dependent mothers is needed. In addition, research to determine effective interventions to support mothers on OMT with breastfeeding is warranted.

### **Conclusion**

The results from this systematic review suggest that breastfeeding has the potential to improve NAS outcomes, including a decreased incidence of pharmacologic need for NAS treatment, a shorter duration of pharmacotherapy, a reduction in hospital stay, and reduced NAS severity and time to withdrawal. While the studies consistently report improved NAS outcomes, challenges exist in this population, and consideration to a mother's poly-substance use and other contraindications for breastfeeding are necessary, in conjunction with the promotion of this feeding method.

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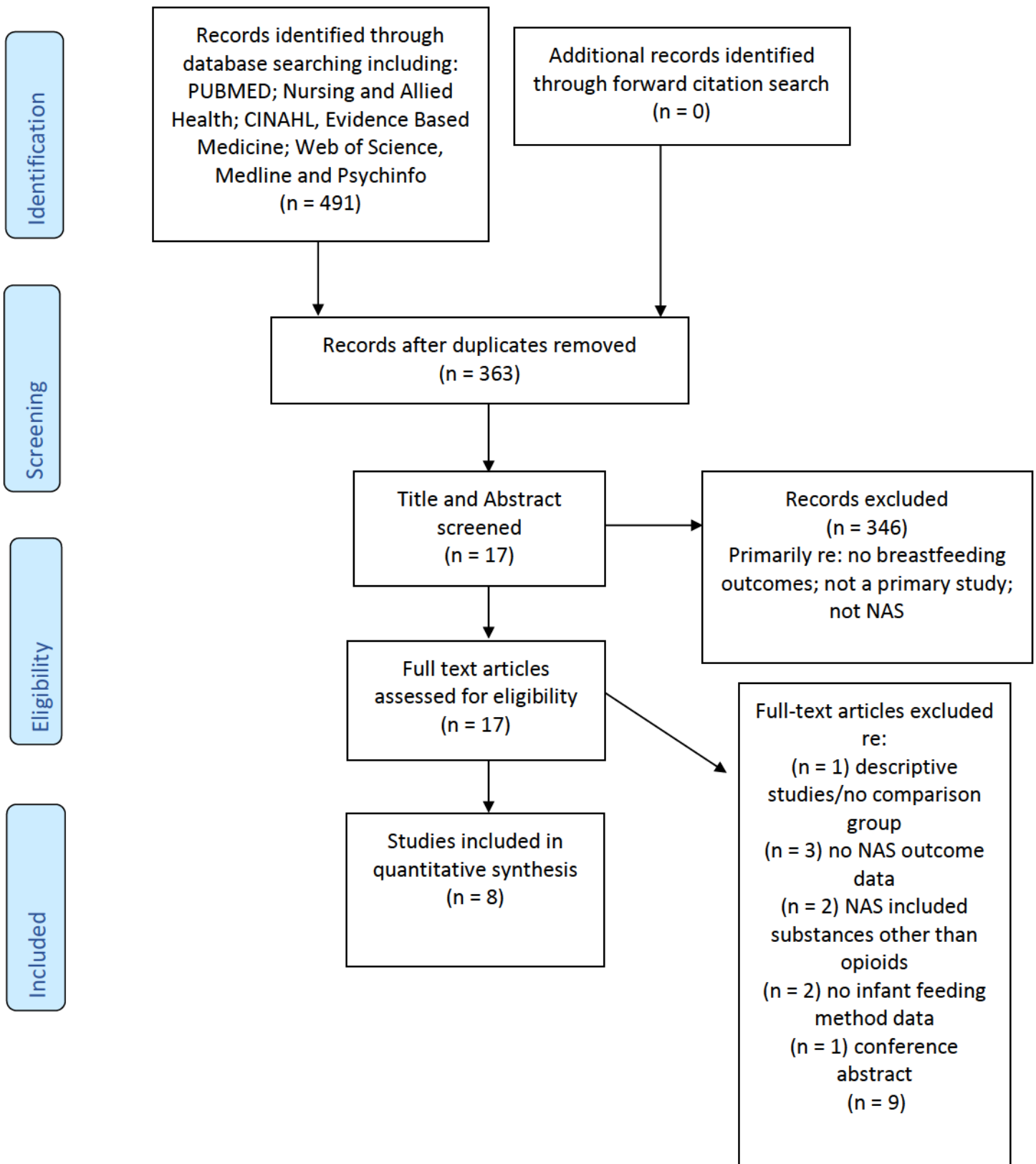
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Fig 1. Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram



Appendix I – JBI Critical Assessment of Selected Articles – Comparable Cohort/Case Control

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Abdel-Latif et al. (2006)	N	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	9/10
Isemann et al. (2011)	N	N	Y	Y	Y	Y	Y	Y	Y	N/A	Y	8/10
Jansson et al. (2008)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	10/10
Lui et al. (2015)	N	Y	Y	Y	Y	Y	U	Y	Y	N/A	Y	8/10
McQueen et al. (2011)	N	Y	Y	Y	U	Y	N	Y	Y	N/A	U	6/10
O'Connor et al. (2013)	N	Y	Y	Y	N	Y	N	Y	Y	N/A	Y	7/10
Welle-Strand et al. (2013)	N	N	Y	Y	Y	Y	N	Y	Y	N/A	Y	7/10
Total (%)	14.3	71.4	100	100	71.4	100	42.9	100	100	N/A	85.7	

Appendix II – JBI Critical Assessment of Selected Articles – Randomized Controlled Trials

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
MacVicar et al. (2018)	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	Y	9/13
Total (%)	100	100	100	0	0	0	100	0	100	100	100	100	100	

Appendix A – Study Characteristics of Included Studies

Author/ Year	Study Design/ Country	Purpose of Study	Feeding Method Defined	Sample	Feeding Method	% Sample Breast- feeding	In Utero Opioid Exposure	Infant Treatment	Quality Appraisal / Risk of Bias
Abdel-Latif et al. (2006)	Retrospective Cohort Review in Australia	Assess the effects of breast milk on the severity and outcome of neonatal abstinence syndrome	Categorized based on predominant method of feeding on the 5 <sup>th</sup> day of life; >2 feeds of formula during the 5 <sup>th</sup> day were classified as formula-fed	190	Breastfed (n=85) Formula-fed (n=105)	45%	Methadone	Morphine, Phenobarbitol	Low
Isemann et al. (2010)	Retrospective Cohort Review in United States	Identify maternal and neonatal factors that impact response to methadone therapy for neonatal abstinence syndrome	Not Specified	128	Breastfed (n=75) Formula-fed (n=53)	59%	Methadone	Methadone, Phenobarbitol	Low
Jansson, et al. (2007)	Matched Design in United States	To evaluate concentrations of methadone in breastmilk among breastfeeding women in a sample of methadone maintained breastfeeding women and a matched group of formula-feeding women	Categorized by mothers expressing a desire to breastfeed exclusively at obstetric care visits. Women were then matched with respect to race, age, and methadone dose within 10mg and desire to bottle-feed exclusively.	16	Breastfed (n=8) Formula-fed (n=8)	50%	Methadone	Not Specified	Low
Lui et al. (2015)	Retrospective Cohort Review in Australia	To compare the impact of different feeding modalities on the onset of NAS	Categorized based on predominant method of feeding during the first 2 days of life. Breastfeeding group ≥50% of daily feeds; Expressed Breastmilk ≥15ml of expressed breastmilk and breastfed < 3 times per day; Formula-fed group ≥50% of daily feeds and minimal EBM (<15ml/day)	194	Breastfed (n=32) Expressed Breastmilk (EBM) (n=12) Formula-fed (n=150)	23%	Methadone	Morphine	Low



MacVicar et al. (2017)	Mixed Methods Pilot Study in Scotland Randomized Controlled Trial and Maternal Questionnaire	To explore the feasibility of in-hospital, tailored breastfeeding support for the substance-exposed mother and infant. Secondary analysis of feeding method and NAS severity	Breastfeeding defined as feeding at breast, ongoing attempts to latch onto breast, and expressed breastmilk for >50% of oral intake on 5 <sup>th</sup> day	14	Breastfed (n=11) Formula-fed (n=3)	79%	Methadone, Buprenorphine	Not Specified	Low
McQueen et al. (2011)	Retrospective Cohort Review in Canada	To determine whether neonatal abstinence scores of infants exposed to methadone in utero differed by infant feeding method	Breastfeeding defined as more than 75% of all feedings; Combination feeding defined as breastfeeding 75% or less, but 25% or greater of all feedings; Formula-feeding defined as breastfeeding less than 25% of all feedings	28	Breastfed (n=8) Combination-Fed (n=11) Formula-fed (n=9)	29%	Methadone	Not Specified	Moderate
O'Connor et al. (2013)	Retrospective Cohort Review in United States	To describe breastfeeding rates among opioid-dependent women and to determine whether breastfeeding is related to the duration, severity, and frequency of pharmacologic treatment for NAS	Breastfeeding defined as infants who were receiving breastmilk at birth and continued to receive breastmilk 6-8 weeks postpartum, even if these infants were also given formula	85	Breastfed (n=65) Formula-fed (n=20)	76%	Buprenorphine	Phenobarbital	Moderate
Welle-Strand et al. (2013)	Retrospective 1999 - 2003 (n=36) Prospective 2005 - 2007 (n=36) and Retrospective 2004 - 2009 (n=52) Cohort Study in Norway	To examine the rate and duration of breastfeeding in a cohort of women in opioid maintenance treatment and the effect of breastfeeding on the incidence and duration of NAS	Self-reported initiation, continuation, and termination of breastfeeding.	124	Breastfed (n=95) Formula-fed (n=29)	77%	Methadone, Buprenorphine	Diluted tincture of opium, Oral Morphine	Moderate

Appendix B – NAS Outcomes

Author/ Year	Pharmacology		Length of Stay	NAS Severity	
	Treatment	Duration		Scores	Time to Withdrawal
Abdel-Latif et al. (2006)	Breastfed infants were less likely to require pharmacologic treatment (45 of 85 infants; 52.9%) compared to formula-fed (83 of 105 infants; 79.0%), $p < .001$	Breastfed infants had a shorter <i>mean</i> duration of NAS treatment (85 days $\pm$ 71.7) compared to formula-fed (108.2 days $\pm$ 81.8; $p = .185$ )	Breastfed infants had a shorter <i>mean</i> hospital stay (14.7 days $\pm$ 14.9) compared to formula fed (19.1 days $\pm$ 15.0; $p = .049$ )	<i>Mean</i> Finnegan Scores for the first 9 days of life were lower in breastfed infants compared to formula-fed ( $p < .05$ )	<i>Median</i> time to withdrawal occurred later in breastfed infants (10 days) compared to formula-fed (3 days; $p < .001$ )
Isemann et al. (2010)	Not Evaluated	Breastfed infants had a shorter <i>median</i> duration of methadone pharmacotherapy (10.8 days) compared to formula-fed (12.4 days; $p < .35$ ). Result not statistically significant.	Breastfed infants had a shorter <i>median</i> hospital stay (12.5 days; ranging from 3-51 days) compared to formula-fed (18.5 days; ranging from 9 to 43 days; $p = .01$ )	Not Evaluated	Not Evaluated
Jansson et al. (2007)	Breastfed infants were less likely to require pharmacologic treatment (1 of 8 infants; 12%) compared to formula-fed (4 of 8 infants; 50%), $p = .28$	Not Evaluated	Not Evaluated	Not Evaluated	Not Evaluated
Lui et al. (2015)	No statistical difference in the incidence of pharmacologic need for NAS treatment for breastfed (23 of 32 infants; 72%), expressed breast milk (12 of 12 infants; 100%) and formula-fed (121 of 150 infants; 81%), $p = .11$	Not Evaluated	Not Evaluated	No statistical difference in <i>mean</i> NAS scores of breastfed infants (5.1 $\pm$ 1.3), expressed breast milk (5.7 $\pm$ 0.9) and formula-fed (5.4 $\pm$ 1.1), $p = 0.47$	Breastfeeding during the first 2 days of life was associated with a delayed onset of NAS ( $p = 0.04$ ). Cox Regression Analysis used to determine variables predictive of time to onset of NAS among infants of MMT mothers.

<p>MacVicar et al. (2017)</p>	<p>Breastfed infants were less likely to require pharmacologic treatment (3 of 11 infants; 27%) compared to formula-fed (3 of 3 infants; 100%). P value not reported.</p>	<p>Not Evaluated</p>	<p>Breastfed infants had a shorter <i>mean</i> hospital stay (<math>10.8 \pm 6.7</math> days) compared to formula-fed infants (<math>30.0 \pm 11.8</math> days). P value not reported.</p>	<p>Not Evaluated</p>	<p>Not Evaluated</p>
<p>McQueen et al. (2011)</p>	<p>Breastfed infants were less likely to require pharmacologic treatment (17%) compared to formula-fed (38.8%) and combination-fed (40.2%)</p>	<p>Not Evaluated</p>	<p>Not Evaluated</p>	<p>Breastfed infants had a lower <i>mean</i> number Finnegan scores recorded (<math>25 \pm 23.5</math>) compared to combination-fed (<math>56.2 \pm 39.1</math>) and formula-fed (<math>95.9 \pm 34.69</math>; <math>p = .001</math>)</p> <p><i>Mean</i> Finnegan Scores were lower in breastfed infants (<math>4.9 \pm 2.9</math>) compared to combination-fed (<math>6.5 \pm 3.7</math>) and formula-fed (<math>6.9 \pm 4.2</math>; <math>p = .0001</math>)</p> <p>Breastfed infants had a lower <i>mean</i> area Finnegan Score (<math>7.7 \pm 3.5</math>) compared to combination-fed (<math>12.4 \pm 4.2</math>) and formula-fed (<math>11.4 \pm 2.9</math>; <math>p = .04</math>)</p>	<p>Not Evaluated</p>
<p>O'Connor et al. (2013)</p>	<p>Breastfed infants were less likely to require pharmacologic treatment (15 of 65 infants; 23%) compared to formula-fed (6 of 20 infants; 30%), <math>p = .56</math></p>	<p>Not Evaluated</p>	<p>Breastfed infants had a variable <i>mean</i> hospital stay (<math>7.08</math> days <math>\pm 4.4</math>) compared to formula-fed (<math>6.6 \pm 1.7</math>; <math>p = .35</math>) due to complications unrelated to NAS. No conclusions drawn.</p>	<p><i>Mean</i> Finnegan peak scores was lower in breastfed infants (<math>8.83 \pm 3.56</math>) compared to formula-fed (<math>9.65 \pm 2.58</math>; <math>p = .17</math>)</p> <p><i>Mean</i> Finnegan time to peak scores was shorter in breastfed infants (<math>66.5 \pm 43.8</math>) compared to formula-fed (<math>73.5 \pm 41.82</math>; <math>p = .32</math>)</p>	<p>Not Evaluated</p>

				<p>Breastfed infants were less likely to score 8 or above on Finnegan tool (65%) compared to formula-fed (75%), p = NS)</p> <p>Breastfed infants were less likely to score 12 or above on Finnegan tool (17%) compared to formula-fed (30%), p = NS)</p>	
Welle-Strand et al. (2013)	<p>Breastfed infants in the methadone-exposed group were less likely to require pharmacologic treatment (44 of 95 infants; 53%) compared to formula-fed (23 of 29 infants; 80%), p = &lt;0.05)</p> <p>For buprenorphine-exposed infants, no difference was found in the incidence of pharmacologic need for NAS treatment for breastfed (61 of 95 infants; 64%) compared to formula-fed infants (13 of 29 infants; 44%), p = NS)</p>	<p>Breastfed infants of women in OMT had a shorter <i>mean</i> duration of NAS treatment (28.6 days ± 19.1) compared to formula-fed (46.7 days ± 26.3; p = &lt;0.05)</p> <p>Breastfed infants of women in MMT had a shorter <i>mean</i> duration of NAS treatment (31 days ± 21.4) compared to formula-fed (48.9 days ± 27.2; p = &lt;0.05)</p> <p>For buprenorphine-exposed infants, no difference was found in duration of NAS treatment for breastfed infants (25.7 days ± 16.0) compared to formula-fed (38.8 days ± 24.0; p = NS)</p>	Not Evaluated	Not Evaluated	Not Evaluated