JOGNN

REVIEW

Integrated Review of the Assessment of Newborns With Neonatal Abstinence Syndrome

Sharon G. Casavant, Taylor Meegan, Mollie Fleming, Naveed Hussain, Semih Gork, and Xiaomei Cong

Correspondence
Xiaomei Cong, PhD, RN, FAAN, University of Connecticut, School of Nursing, 231 Glenbrook Rd., U-2026, Storrs, CT 06269.
xiaomei.cong@uconn.edu

Keywords
console
eat
epigenetics
Finnegan scale
neonatal abstinence syndrome
pharmacokinetics
Sleep

ABSTRACT

Objective: To critically review and summarize current knowledge regarding the assessment of newborns with neonatal abstinence syndrome (NAS).

Data Sources: We searched the following databases for articles on the assessment of newborns with NAS that were published in English between January 2014 and June 2020: PubMed, CINAHL, and PsycINFO. Keywords and Medical Subject Heading terms used to identify relevant research articles included *neonatal abstinence syndrome*; *Finnegan Scale*; *eat, sleep, console*; *epigenetics*; *genetics*; *pharmacokinetics*; and *measurement*. We independently reviewed articles for inclusion.

Study Selection: We retrieved 435 articles through database searches and 17 through manual reference searches; 31 articles are included in the final review. Excluded articles were duplicates, not relevant to NAS, qualitative studies, and/or of low quality.

Data Extraction: We used the methodology of Whittemore and Knafl to guide this integrative review. We extracted and organized data under the following headings: author, year and country, purpose, study design, participants, measurement, biomarker (if applicable), results, limitations, recommendations, and intervention.

Data Synthesis: The Finnegan Neonatal Abstinence Scale is the most widely used instrument to measure symptoms of NAS in newborns, although it is very subjective. Recently, there has been a transition from the Finnegan Neonatal Abstinence Scale to the eat, sleep, console method, which consists of structured assessment and intervention and has been shown to decrease length of hospital stay and total opioid treatment dose. Researchers examined biomarkers of NAS, including genetic markers and autonomic nervous system responses, on the variation in incidence and differential severity of NAS. In the included articles, women with opioid use disorder who were treated with naltrexone during pregnancy gave birth to newborns without NAS diagnoses. However, most women who were treated with buprenorphine gave birth to newborns with NAS diagnoses.

Conclusion: NAS negatively affects newborns in a multitude of ways, and the objective assessment and measurement of the newborn's response to withdrawal remains understudied and needs further investigation.

JOGNN, ■, ■–■; 2021. https://doi.org/10.1016/j.jogn.2021.04.014

Accepted May 2021;

Sharon G. Casavant, PhD, RN, is a postdoctoral fellow and adjunct faculty, University of Connecticut, School of Nursing, Storrs, CT.

Taylor Meegan, BS, RN, is a PhD student, University of Connecticut, School of Nursing, Storrs, CT.

(Continued)

Over the past decade, the opioid use epidemic among pregnant women in the United States has risen threefold, and an estimated 6% of pregnant women are currently diagnosed annually with opioid use disorder (Center for Behavioral Health Statistics and Quality, 2015). Persistent exposure to opioids and other similar drugs during pregnancy often leads to a spectrum of withdrawal symptoms for the newborn, and these symptoms are referred to as neonatal abstinence syndrome (NAS) or, more specifically, neonatal opioid withdrawal syndrome when only opioids are the causative agents. For the purpose of this review, we use the more general term *NAS* to refer to a constellation of symptoms defined by central nervous system dysregulation, gastrointestinal disorders, autonomic dysregulation, and respiratory abnormalities (Allocco et al., 2016; Kocherlakota, 2014). The prevalence of NAS secondary to opioid withdrawal is 7.3 per 1,000 births nationally (Brown et al., 2016). Newborns who experience the effects of NAS also have associated problems, such as greater rates of birth defects

REV 5.6.0 DTD ■ JOGN612_proof ■ 8 June 2021 ■ 9:46 am ■ ce

Data on long-term outcomes for newborns with neonatal abstinence syndrome are limited and an important area of future research.

(Fornoff & Sandidge, 2020) and altered brain development, that have lifelong effects (Monnelly et al., 2019). Therefore, it is essential that withdrawal is accurately assessed and carefully managed with the appropriate use of medication and properly monitored weaning, stress is avoided, and a smooth transition from drug dependence to drug desensitization is promoted. Therefore, the purpose of this review was to critically review and summarize current knowledge regarding the assessment of newborns with NAS.

Methods

Design

We used the integrative review method of Whittemore and Knafl (2005), which is a systematic approach to problem identification, literature search, data evaluation, and data analysis. The initial step of the integrative review is to identify the problem and determine important variables to conduct the literature search. The literature search focused on all relevant literature, using multiple databases to provide the best primary source retrieval. The data analysis stage required data reduction, display, and comparison as well as the extraction of data into previously established criteria and subgroups. The results of the analysis are provided in table format to allow for the comparison and contrast of studies and to facilitate synthesis (see Supplemental Tables S1–S4). The final step of an integrative review is to develop conclusions regarding the represented data.

Data Sources and Search

Study selection. On June 11, 2020, we conducted a comprehensive literature search of the PubMed, CINAHL, and PsycINFO databases to identify primary research articles that focused on how NAS is assessed as well as how it influences newborns behaviorally, biophysically, epigenetically, and pharmacokinetically. Keywords used to identify relevant research articles included *neonatal abstinence syndrome*; *NAS*; *assessment*; *evaluation*; *Finnegan scale*; *eat, sleep, console; epigenetics*; *genetics*; *pharmacokinetics*; *methadone*; *buprenorphine*; *naltrexone*; *genomic*; and *measurement*. The Medical Subject Heading terms *neonatal abstinence syndrome* AND *measurement*; *neonatal abstinence syndrome* AND *methadone*; and *neonatal opioid withdrawal syndrome* AND *genomic* were included in the search on PubMed. Keywords were combined using "and," "or," and "and/or." Manual searches were also completed of the references from previously published studies and literature reviews.

Data extraction. Articles were eligible for inclusion if they reported primary research studies; were published within the last 6 years (2014–2020, the time span in which NAS became more widely reported in the research literature); focused on NAS assessment and how the syndrome influences the newborn behaviorally, biophysically, epigenetically, and pharmacokinetically; and were written by researchers in English. Articles were excluded if they were reviews, study protocols, and/or case studies. The first three authors (S.G.C., T.M., and M.F.) conducted a database search that was also verified by the sixth author (X.C.). The third author (M.F.) retrieved the articles via these search methods and reviewed them for duplication.

Assessment of Methodologic Quality

Although it is not essential to calculate quality scores for integrative review methods, the first and second authors used a scale based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (von Elm et al., 2007). The STROBE instrument contains 22 items. The first two authors (S.G.C. and T.M.) assessed each article and assigned 1 point if the item was present or 0 if it was not. The first two authors resolved disagreements through discussion among the first three authors. The first three authors agreed that articles that scored less than 20 points should be excluded ($n = 9$). Thus, 31 articles were included in this review.

Data Synthesis

Each author read the full texts of the 31 included articles. The third author used a standardized extraction form to extract data related to the author, year of publication, objective, study design, population studied, outcomes, biological markers, data source, and results. We discussed the findings and agreed on the synthesis and analysis.

Results

Description of the Included Studies

The search and study selection processes are depicted in the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) flowchart (Moher et al., 2009; see Figure 1). The

Mollie Fleming is a BS student, University of Connecticut, Department of Mathematics, Storrs, CT.

Naveed Hussain, MD, is a professor, University of Connecticut, School of Medicine, Department of Pediatrics and a neonatologist, Connecticut Children's Medical Center at UConn Health Center, Hartford, CT.

Semih Gork, MD, is the Vice Chief of Pediatrics, The Hospital of Central Connecticut, New Britain, CT.

Xiaomei Cong, PhD, RN, FAAN, is a professor and Associate Dean for Research, University of Connecticut, School of Nursing, Storrs, CT.

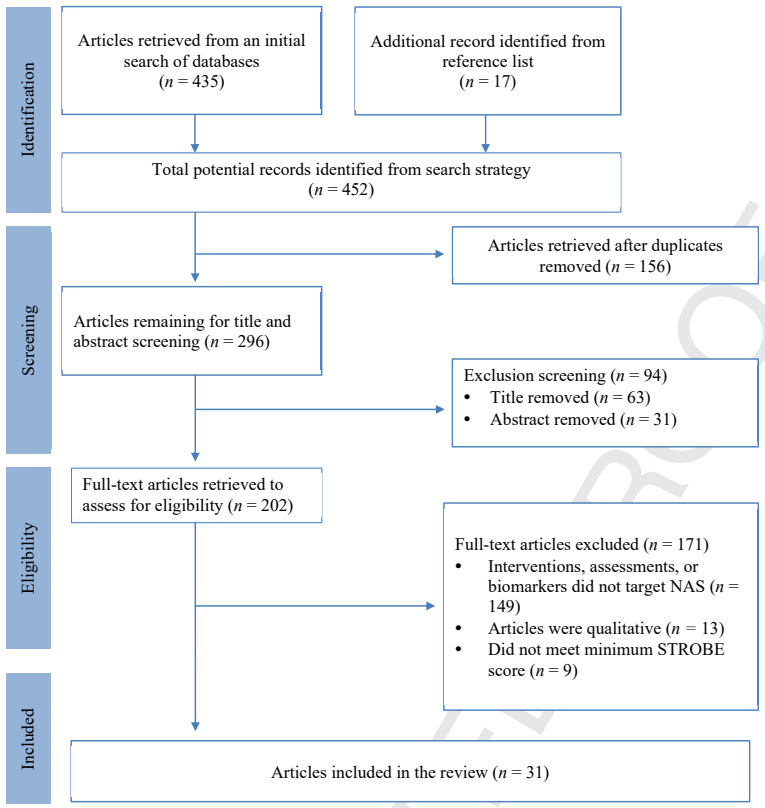

Figure 1. Diagram of study selection for the integrative review. NAS = neonatal abstinence syndrome; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology.

preliminary search yielded 452 research articles. After the removal of duplicates and the application of exclusion criteria, we reviewed the titles and abstracts of 249 articles and excluded 204. After final assessment of eligible full-text articles, 31 were included in our review (see Supplemental Tables S1–S4). Of the identified studies, 28 were conducted in the United States, including Connecticut (Grossman et al., 2017, 2018); Kentucky and Pennsylvania (Gomez-Pomar et al., 2017); Maine (Heller et al., 2017); Maine and Massachusetts (Wachman et al., 2015); Maryland (Liu et al., 2016); Massachusetts (Allocco et al., 2016; Timpson et al., 2018; Wachman et al., 2013, 2019; Wachman, Grossman, et al., 2018; Wachman, Hayes, et al., 2018); New Hampshire (Holmes et al., 2016); New Mexico (Achilles & Castaneda-Lovato, 2019); New York (Levran et al., 2014); North Carolina (Blount et al., 2019; Dodds et al., 2019); Ohio (Hall et al., 2015; Wiles et al., 2015); Pennsylvania (Kraft et al., 2017; Lemon et al., 2018; Moore et al., 2018; Ng et al., 2015; Oji-Mmuo et al., 2016); Texas (Tolia et al., 2018); Washington (Parlaman et al., 2019); and seven sites combined into three categories: U.S. urban areas, U.S. rural areas, and Europe (Jones et al., 2016). One study was conducted in Canada (Chisamore et al., 2016), one in Germany (Schubach et al., 2016), and one in Iran (Fanaei et al., 2020). Q3

The sample sizes of the included studies ranged from 12 newborns (Schubach et al., 2016) to 3,364 newborns (Tolia et al., 2018). Of the included studies, 17 were descriptive cohort studies, and 9 were quasiexperimental studies that did not include randomization or a control group. The remaining 5 studies were randomized controlled trials.

We classified results as studies with the Finnegan Neonatal Abstinence Scale to measure NAS responses (n = 7); studies with autonomic nervous system response such as skin conductance (n = 2) or genetic and related biomarkers to Q4 measure NAS responses (n = 5); studies with pharmacologic treatment and pharmacokinetic (PK) profiles to measure and manage NAS responses (n = 9); and studies with the eat,

sleep, console (ESC) method to measure and manage NAS responses ($n = 8$).

Finnegan Neonatal Abstinence Scale

The most widely used tool to evaluate NAS in newborns was the Finnegan Neonatal Abstinence Scale; we reviewed seven studies related to this scale. This score is based on the observation of more than 30 clinical withdrawal signs that are subjectively rated by a trained nurse or physician every 3 to 4 hours. The subjectivity of the score may instill bias in the assessment. A newborn who scores greater than 8 at one assessment or greater than 12 over two assessments is typically given medication. A number of researchers have recently focused on developing more objective scoring methods for treatment. However, the Finnegan Neonatal Abstinence Scale is still used for clinical assessment of 52% to 65% of newborns with NAS (Jones et al., 2016).

Two research teams focused on increasing knowledge to improve accuracy in scoring newborns using the Finnegan Neonatal Abstinence Scale (Holmes et al., 2016; Timpson et al., 2018). As a result, the average length of stay (LOS) for morphine-treated newborns decreased, and the cumulative morphine dose decreased (Holmes et al., 2016). In 2018, Timpson et al. conducted a quality improvement study in which nurses participated in a single-session withdrawal-assessment program that incorporated education, scoring guidelines, and a restructured Finnegan Neonatal Abstinence Scale. Participants scored a standardized videorecorded newborn who presented with opioid withdrawal before and after training. After training, twice as many participants scored the videorecorded newborn accurately compared to how they scored before training (Timpson et al., 2018). Universal education and guidelines on using the Finnegan Neonatal Abstinence Scale can be used to increase accuracy and consistency when assessing NAS symptoms in newborns. Gomez-Pomar et al. (2017) conducted an analysis of score variation attributable to nurses. The proportions of variation in scores that was attributable to individual nurses were 9.8% and 5.1% in two different hospital units, respectively. Thus, the researchers concluded that there were minimal extraneous influences in the actual scores, which supported the continued use of the Finnegan Neonatal Abstinence Scale (Gomez-Pomar et al., 2017).

Researchers at a single tertiary care center in the United States analyzed the reliability of the Finnegan Neonatal Abstinence Scale by comparing NAS symptoms in preterm newborns versus full-term newborns exposed to methadone (Allocco et al., 2016). They found a large variation in symptoms between term and preterm newborns. Their findings indicated that although the Finnegan Neonatal Abstinence Scale may be a relatively reliable tool for term newborns, extensive training in administering the scale and/or development of a more objective assessment tool for exposed preterm newborns is needed for consistency in symptom identification.

Autonomic Nervous System Response

Skin conductance. An interesting and novel approach to assessing distress in newborns with NAS is the use of skin conductance ($n = 2$). Opioid withdrawal often causes newborns to have heightened autonomic nervous system activity, which precipitates many of the symptoms associated with NAS (Storm et al., 2002). Autonomic nervous system stimulation provokes the newborn to have increased sweat production, which is measured using a two-electrode biosignal recorder that is used to evaluate the conductance level of the skin on the pads of the feet. Oji-Mmuo et al. (2016) found that newborns who required pharmaceutical treatment in the first 72 hours of life had a greater baseline conductance before heel lance for blood sampling. These same newborns had a decreased difference between peak and baseline conductance during the heel lance. Similarly, Schubach et al. (2016) found greater values in skin conductance measures in newborns diagnosed with NAS. The potential to indicate elevated stress levels in newborns with NAS through skin conductance should be further investigated.

Genetic biomarkers. Researchers who conducted genetic testing in newborns with NAS discovered that certain alleles found in newborns were correlated with increased LOS and increased prevalence of multipharmaceutical treatment (Wachman et al., 2015). In addition, other alleles were correlated with decreased LOS (Wachman et al., 2013, 2015). There are still other alleles in women that correlated with increased LOS and multipharmaceutical treatment for their newborns (Wachman et al., 2015). Although research continues to be lacking in this area, researchers have targeted possible physiologic processes as important to investigate in the relationship of women's dosage, placental transfer, and newborns' metabolism of opioids. These

REV 5.6.0 DTD ■ JOGN612_proof ■ 8 June 2021 ■ 9:46 am ■ ce

include the cytochrome p450 pathway, which is a superfamily of enzymes important in drug metabolism, as well as single nucleotide polymorphisms (SNPs) found in the following genes: *CYP3A*, *CYP2C8* (important in the metabolism of many common opioids), *CYP2D6* (important in oxycodone metabolism and varying in expression among people of different racial backgrounds), and *MDR1* expression on the placenta (due to a correlation between MDR1 levels and fetal methadone levels; Wachman et al., 2015).

Single nucleotide polymorphisms. Researchers discovered that specific SNPs in key candidate genes, such as the μ-opioid receptor (*OPRM1*) and catechol-*O*-methyltransferase (*COMT*) genes, contribute to the variability and severity of NAS (Wachman et al., 2013, 2015). In one study, researchers examined NAS severity and found that women with greater levels of methylation on the *OPRM1* gene gave birth to newborns who often had greater levels of methylation on that gene and required pharmacologic interventions to decrease distress yielding, longer LOSs for newborns (Wachman et al., 2018). In addition, two research teams (Levran et al., 2014; Moons et al., 2014) discovered that the variations of SNPs rs53576 and rs237902 in the oxytocin receptor gene (*OXTR*) were also associated with cocaine addiction and emotional stress responses in adults. Although researchers have shown that these genotyping factors are altered in adult populations who are withdrawing from cocaine, little research has focused on how these factors affect vulnerable newborns whose mothers used opioids during pregnancy.

Brain-derived neurotrophic factor and nerve growth factor. Iranian researchers investigated the effect of opium addiction in pregnant women on brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) levels in maternal and umbilical cord blood (Fanaei et al., 2020). Additionally, opium use during pregnancy was associated with significantly greater adverse pregnancy outcomes. Thus, this study suggests that lower levels of BDNF and NGF due to opium use may lead to neurodevelopmental disorders in newborns and worse pregnancy outcomes (Fanaei et al., 2020).

Pharmacologic Assessment and Treatment Methods

Methadone, buprenorphine, morphine, and phenobarbital. Historically, methadone or buprenorphine has been recommended for the treatment of opioid dependence in pregnant women (Klaman et al., 2017; Wachman et al., 2019). Tolia et al. (2018) and Lemon et al. (2018) found that newborns exposed to buprenorphine before birth were less likely to receive pharmacotherapy for NAS treatment than newborns exposed to methadone before birth. Toila et al. (2018) further found that exposure to buprenorphine during the prenatal period resulted in shorter lengths of hospital stay for newborns compared to newborns exposed to methadone during the prenatal period (Tolia et al., 2018). In a 2019 study, Wachman and colleagues examined pregnancy and neonatal outcomes in women treated with naltrexone versus women treated with buprenorphine. Among the 18 woman–newborn dyads, these researchers discovered that women who were treated with naltrexone gave birth to newborns who were not diagnosed with NAS. Conversely, 92% of newborns born to women treated with buprenorphine were diagnosed with NAS.

In the United States, newborns who require pharmacotherapy for NAS receive morphine for treatment more than 80% of the time (Kraft et al., 2017; Patrick et al., 2015). In a study to compare the efficacy of sublingual buprenorphine and oral morphine for the treatment of NAS, Kraft et al. (2017) found that the median duration of treatment for the buprenorphine group was significantly shorter than the median duration of treatment in morphine group, as was the median LOS. In addition, adjunctive phenobarbital was administered to 15% of newborns in the buprenorphine group and to 23% of newborns in the morphine group (Kraft et al., 2017). When comparing the efficacy of morphine versus methadone, researchers determined that methadone was associated with a 14% decrease in LOS for newborns compared to morphine (Davis et al., 2018). Additionally, when comparing morphine administration based on symptomology versus a weight-based dosing model (i.e., 1 mg morphine per kilogram), Chisamore et al. (2016) found that newborns in the weight-based dosing model had shorter LOSs. Conversely, another group of researchers investigated the benefits of treating NAS with a novel symptom-triggered methadone approach rather than a fixed-schedule methadone dose-tapering approach (Wachman et al., 2019). Newborns who received methadone based only on symptoms experienced a reduced median LOS (10.5 vs. 17.0 hospital days). Hall et al. (2015) conducted a retrospective, multisite cohort analysis to examine

Mitigating the negative sequelae of neonatal abstinence syndrome requires the implementation of a management protocol and standardized scoring system to inform medication initiation, maintenance, and weaning.

the outcomes of a consensus protocol, including standardized guidelines for scoring NAS, nonpharmacologic treatment, triggers for implementation, guidelines for adjunctive therapy, and a stringent weaning protocol across six hospitals in Ohio. They found that implementing a stringent weaning protocol also decreased the duration of opioid treatment and LOS for newborns (Hall et al., 2015).

PK profiles of medications used to treat NAS. Several researchers (Liu et al., 2016; Moore et al., 2018; Ng et al., 2015; Wiles et al., 2015) investigated the PK profiles of medications used to treat NAS in newborns to evaluate dosing strategies. Ng et al. (2015) conducted a retrospective population PK analysis of (a) newborns with NAS treated with sublingual buprenorphine versus oral morphine in randomized, double-blinded clinical study and (b) data from healthy adults from a previously published PK study. This PK analysis found that the clearance of buprenorphine was linearly related to body weight. Moore et al. (2018) also conducted a randomized controlled trial to assess the efficacy of buprenorphine and morphine. Their results indicated that the time to NAS stabilization decreased with increasing buprenorphine exposure, which was also confirmed by other researchers in this section of our results (Moore et al., 2018). Thus, their model quantified a PK–pharmacodynamic relationship of buprenorphine in NAS and provided dosing strategies for future clinical trials (Moore et al., 2018). Similarly, Wiles et al. (2015) sought to determine the volume of distribution and clearance of oral methadone using PK profiles. They found that a one-compartment model with first-order absorption best described blood concentrations of methadone. They recommended optimal dosing strategies that included a starting dose of 0.1 mg/kg per dose every 6 hours for most newborns who require pharmacologic treatment for NAS followed by an expedited weaning phase (Wiles et al., 2015). Liu et al. (2016) evaluated the PK properties of oral morphine to assess different doses and dosing regimens in newborns with NAS. Findings included an estimated first-order absorption rate constant and bioavailability of 0.0751 hours and 48.5%, respectively. Therefore, the researchers concluded that the population PK model for oral morphine is reasonable and acceptable (Liu et al., 2016).

The ESC Approach

In 2017, Grossman and colleagues devised a novel approach to treating newborns with NAS that included family involvement called the ESC approach (Grossman et al., 2018). With this approach, nurses conduct a structured assessment of a newborn's feeding, sleep duration between feedings, and ability to be consoled. If the newborn can eat and sleep, regardless of Finnegan Neonatal Abstinence Scale, then pharmacologic management is not used. Grossman and colleagues identified the guidelines that are used for evaluation:

- Eat: The newborn's ability to breastfeed successfully or eat at least 1 oz per feeding.
- Sleep: The newborn's ability to sleep undisturbed for a minimum of 1 hour. Being held by a parent may facilitate better sleep.
- Console: The newborn's ability to be consoled within 10 minutes. If the newborn is not consoled, additional nonpharmacologic interventions should be attempted, including having a second caregiver console. If the newborn is inconsolable, pharmacologic intervention may be considered.

In recent years, several researchers conducted studies on the use of the ESC approach compared to the Finnegan Neonatal Abstinence Scale to decrease length of hospital stay, total opioid treatment, and treatment dose administered for newborns with NAS. In five studies, researchers found significant decreases in the LOS for newborns diagnosed with NAS with use of the ESC approach (Achilles & Castaneda-Lovato, 2019; Blount et al., 2019; Dodds et al., 2019; Parlaman et al., 2019; Wachman, Grossman, et al., 2018). Furthermore, in three of these studies, the number of newborns diagnosed with NAS who required pharmacologic treatment decreased significantly (Blount et al., 2019; Grossman et al., 2019; Wachman, Grossman, et al., 2018). Among newborns who required pharmacologic intervention, four teams of researchers discovered that the ESC approach decreased the cumulative doses required for treatment (Achilles & Castaneda-Lovato, 2019; Blount et al., 2019; Dodds et al., 2019; Parlaman et al., 2019). Thus, switching from a Finnegan Neonatal Abstinence Scale to an ESC system can

REV 5.6.0 DTD ■ JOGN612_proof ■ 8 June 2021 ■ 9:46 am ■ ce

decrease the length of hospital stay and decrease the total amount of pharmacologic treatment for newborns with NAS.

Discussion

We found that although the Finnegan Neonatal Abstinence Scale remains the most widely used tool with which to assess the severity of symptoms in newborns diagnosed with NAS, other methods are available. The reliability of the Finnegan Neonatal Abstinence Scale is affected by the subjectivity of the person scoring (Jones et al., 2016). However, reliability can be improved through increased training on how to score and by simplifying the overall scale (Holmes et al., 2016; Timpson et al., 2018). Another challenge when using the Finnegan Neonatal Abstinence Scale is that preterm newborns have the neuronal circuitry required to perceive pain; however, their functional responses are immature (Fitzgerald, 2005). Thus, they do not display the same symptomatic response as full-term newborns with NAS. This is an important area of research that requires further investigation; an instrument that can be used to accurately assesses NAS symptoms in preterm newborns is needed.

Skin conductance offers an objective method to assess NAS symptoms in newborns. As mentioned earlier, opioid withdrawal often causes newborns to have heightened autonomic nervous system activity that precipitates many of the symptoms associated with NAS, including emotional sweating. The greater the distress experienced by the newborn, the greater the skin conductance (Oji-Mmuo et al., 2016; Schubach et al., 2016). This novel objective assessment tool has the potential to offer additional insight into the newborn's level of distress and might be a relatively cost efficient way to increase the amount of data available regarding the newborn's experience throughout withdrawal. Collecting salivary cortisol and oxytocin samples may also offer more objective data points related to the level of distress or comfort.

A variety of alleles found in women who were addicted to opioids and their newborns influenced LOS and the need for medication for newborns with NAS, and methylation and SNP variation in *OPRM1* and *OXTR* affected the severity of symptoms (Wachman et al., 2013, 2015; Wachman, Hayes, et al., 2018). Another side effect of opioid use in pregnancy is decreased levels of BDNF and NGF, which often results in negative neurobehavioral or neurodevelopmental sequelae (Fanaei et al., 2020). These findings indicate that multifactorial effects of genetic factors influence the variation in incidence and differential severity of NAS and should be further investigated.

Focusing on pharmacologic treatment for women with addiction to opioids during the antenatal period, researchers found that buprenorphine and naltrexone led to decreased LOS in addition to reduced need for medication (Lemon et al., 2018; Wachman et al., 2019). Thus, antenatal treatment with buprenorphine or naltrexone resulted in easier transitions for the newborn and may influence pharmacologic treatment decisions in the antenatal period. For the newborn with NAS, morphine remains the pharmacologic treatment of choice; however, treatment with buprenorphine or methadone rather than morphine resulted in decreased LOSs (Davis et al., 2018; Kraft et al., 2017; Patrick et al., 2015).

When examining PK profiles with the intention of determining dosing strategies, absorption, and bioavailability, researchers determined that buprenorphine was linearly related to body weight (Ng et al., 2015). Moreover, increasing buprenorphine exposure decreased the time to stabilization for the newborn with NAS (Moore et al., 2018). Wiles and colleagues (2015) determined that the optimized dosing strategy for newborns requiring methadone should be 0.1 mg per newborn kilogram and when appropriate weaning should begin. Liu and colleagues (2016) found that the absorption and bioavailability of morphine among newborns with NAS was reasonable and acceptable. These researchers' findings indicate a number of dosing strategies, although it seems that antenatal and neonatal treatment with buprenorphine is a better option to treat newborns with NAS considering pharmacologic options and PK profiles.

Although pharmacologic options for treating NAS are still used frequently, the implementation of the ESC intervention resulted in a significant decrease in newborns requiring pharmacologic intervention and a reduced LOS in the hospital (Blount et al., 2019). One of the challenges from an implementation perspective is that this ESC intervention typically keeps the woman–newborn dyad in the labor, delivery, postpartum unit of the hospital rather than placing the newborn in a NICU, resulting in increased administrative,

Continued studies on scoring, interventions, and outcomes will benefit the newborn and family and reduce institutional costs.

staffing, and care costs that may put an undue burden on the unit and reduce the number of rooms available to incoming women who may need that particular bed. As such, we suggest a cost comparison by unit administration before implementation.

Limitations

One of the major limitations of this review is that most of the included studies had relatively small sample sizes, and only 11 studies had more than 100 participants. Second, the numerous differences in focus and methodology across the studies limit the generalizability of our findings. Third, we included only studies written in English, which decreases the potential findings.

Implications for Clinicians

Our review sheds light on the antenatal treatment of women who are addicted to opioids and the need for better treatment options for the woman and the newborn using buprenorphine or naltrexone. In addition, assessment options were discussed, including decreasing the subjectivity of the Finnegan Neonatal Abstinence Scale through education. Using objective measures such as skin conductance, cortisol and oxytocin levels, and genetic evaluation for alleles may influence the responses of women with opioid addictions and their newborns. Pharmacologic treatment and PK profiles indicate that buprenorphine or methadone may be better options for treating the newborn with NAS. Finally, the introduction of the ESC intervention offers a nonpharmaceutical assessment and treatment approach that decreases LOS, lessens the need for pharmacologic treatment, and enhances bonding between the woman and her newborn.

Conclusion

Findings from our integrative review enhance what is known about the assessment and treatment methods associated with NAS and newborn outcomes. The evidence suggests that better education for clinicians on assessing the newborn with NAS using the Finnegan Neonatal Abstinence Scale results in more consistent ratings. There is also evidence that the ESC assessment and treatment method not only reduces the LOS and use of medication but also improves parental–newborn bonding, which is critical to newborn mental health and development. Future researchers may focus on identification of the most optimal methods for measuring NAS symptoms and treatment methodologies, whether pharmacologic or holistic in nature. Nurses, key professionals within the antenatal, labor and delivery, and postpartum arenas, should be aware and prepared for the potential perinatal health effects of women with opioid use disorder. As part of interdisciplinary teams, nurses can be leaders in the development and implementation of NAS assessments and treatments, leading to organizational policy changes.

ACKNOWLEDGMENT

Funded by a UConn Institute for Collaboration of Health, Intervention and Policy (InCHIP) Faculty Seed Grant (Cong, X.) and Bio-Genomic Markers for Management of Neonatal Abstinence Syndrome: A Pilot Study, the National Institute of Nursing Research of the National Institutes of Health (NIH-NINR) under award number 1F32 NR018591-01 (Casasvant, S.) and award number 5R01NR016928-02 (Cong, X.).

CONFLICT OF INTEREST

The authors report no conflicts of interest or relevant financial relationships.

FUNDING

None.

REFERENCES

Achilles, J. S., & Castaneda-Lovato, J. (2019). A quality improvement initiative to improve the care of infants born exposed to opioids by implementing the Eat, Sleep, Console assessment tool. *Hospital Pediatrics, 9*(8), 624–631. https://doi.org/10.1542/hpeds.2019-0144

Allocco, E., Melker, M., Rojas-Miguez, F., Bradley, C., Hahn, K. A., & Wachman, E. M. (2016). Comparison of neonatal abstinence syndrome manifestations in preterm versus term opioid-exposed newborns. *Advances in Neonatal Care, 16*(5), 329–336. https://doi.org/10.1097/ANC.0000000000000320

Blount, T., Painter, A., Freeman, E., Grossman, M., & Sutton, A. G. (2019). Reduction in length of stay and morphine use for NAS with the "Eat, Sleep, Console" method. *Hospital Pediatrics, 9*(8), 615–623. https://doi.org/10.1542/hpeds.2018-0238

Brown, J. D., Doshi, P. A., Pauly, N. J., & Talbert, J. C. (2016). Rates of neonatal abstinence syndrome amid efforts to combat the opioid abuse epidemic. *JAMA Pediatrics, 170*(11), 1110–1112. https://doi.org/10.1001/jamapediatrics.2016.2150

Chisamore, B., Labana, S., Blitz, S., & Ordean, A. (2016). A comparison of morphine delivery in neonatal opioid withdrawal. *Substance Abuse: Research and Treatment, 10*(Suppl. 1), 49–54. https://doi.org/10.4137/SART.S34550

Cong, X., Ludington-Hoe, S. M., Hussain, N., Cusson, R. M., Walsh, S., Vazquez, V., & Vittner, D. (2015). Parental oxytocin responses during skin-to-skin contact in pre-term newborns. *Early Human*

Development, 91(7), 401–406. https://doi.org/10.1016/j.earlhumdev.2015.04.012

Davis, J. M., Shenberger, J., Terrin, N., Breeze, J. L., Hudak, M., Wachman, E. M., & Lester, B. (2018, August 1). Comparison of safety and efficacy of methadone vs morphine for treatment of neonatal abstinence syndrome: A randomized clinical trial. *JAMA Pediatrics, 172*(8), 741–748. https://doi.org/10.1001/jamapediatrics.2018.1307

Dodds, D., Koch, K., Buitrago-Mogollon, T., & Horstmann, S. (2019). Successful implementation of the Eat Sleep Console model of care for infants with NAS in a community hospital. *American Academy of Pediatrics, 9*(8), 632–638. https://doi.org/10.1542/hpeds.2019-0086

Fitzgerald, M. (2005). The development of nociceptive circuits. *Nature Reviews Neuroscience, 6*(7), 507–520. https://doi.org/10.1038/nrn1701

Fornoff, J., & Sandidge, T. (2020). Prevalence of birth defects among infants with neonatal abstinence syndrome in Illinois, 2015–2016. *Birth Defects Research, 113*(2), 134–143. https://doi.org/10.1002/bdr2.1792

Gomez-Pomar, E., Finnegan, L. P., Devlin, L., Bada, H., Concina, V. A., Ibonia, K. T., & Westgate, P. (2017). Simplification of the Finnegan Neonatal Abstinence Scoring System: Retrospective study of two institutions in the USA. *British Medical Journal Open, 7*(9), Article e016176. https://doi.org/10.1136/bmjopen-2017-016176

Grisham, L. M., Stephen, M. M., Coykendall, M. R., Kane, M. F., Maurer, J. A., & Bader, M. Y. (2019). Eat, Sleep, Console approach: A family-centered model for treatment of neonatal abstinence syndrome. *Advances in Neonatal Care, 19*(3), 138–144. https://doi.org/10.1097/ANC.0000000000000581

Grossman, M. R., Berkwitt, A. K., Osborn, R. R., Xu, Y., Esserman, D. A., Shapiro, E. D., & Bizzarro, M. J. (2017). An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics, 149*(6), Article e20163360. https://doi.org/10.1542/peds.2016-3360

Grossman, M. R., Lipshaw, M. J., Osborn, R. R., & Berkwitt, A. K. (2018). A novel approach to assessing newborns with neonatal abstinence syndrome. *Hospital Pediatrics, 8*(1), 1–6. https://doi.org/10.1542/hpeds.2017-0128

Hall, E. S., Wexelblatt, S. L., Crowley, M., Grow, J. L., Jasin, L. R., Klebanoff, M. A., & Walsh, M. C. (2015). Implementation of a neonatal abstinence syndrome weaning protocol: A multicenter cohort study. *Pediatrics, 136*(4), e803–e810. https://doi.org/10.1542/peds.2015-1141

Heller, N. A., Logan, B. A., Morrison, D. G., Paul, J. A., Brown, M. S., & Hayes, M. J. (2017). Neonatal abstinence syndrome: Neurobehavior at 6 weeks of age in newborns with or without pharmacological treatment for withdrawal. *Developmental Psychobiology, 59*(5), 574–582. https://doi.org/10.1002/dev.21532

Holmes, A. V., Atwood, E. C., Whalen, B., Beliveau, J., Jarvis, J. D., Matulis, J. C., & Ralston, S. L. (2016). Rooming-in to treat neonatal abstinence syndrome: Improved family-centered care at lower cost. *Pediatrics, 137*(6), Article e20152929. https://doi.org/10.1542/peds.2015-2929

Jones, H. E., Seashore, C., Johnson, E., Horton, E., O'Grady, K. E., Andringa, K., & Holmes, A. V. (2016). *American Journal on Addictions, 25*(5), 370–373. https://doi.org/10.1111/ajad.12388

Klaman, S., Isaacs, K., Leoplold, A., Perpich, J., Hayasi, S., Vender, J., & Jones, H. E. (2017). Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their newborns and children: Literature review to support national guidance. *Journal of Addiction Medicine, 11*(3), 178–190. https://doi.org/10.1097/ADM.0000000000000308

Kocherlakota, P. (2014). Neonatal abstinence syndrome. *Pediatrics, 134*(2), e547–e561. https://doi.org/10.1542/peds.2013-3524

Kraft, W. K., Adeniyi-Jones, S. C., Chervoneva, I., Greenspan, J. S., Abatemarco, D., Kaltenbach, K., & Ehrlich, M. E. (2017). Buprenorphine for the treatment of the neonatal abstinence syndrome. *New England Journal of Medicine, 376*(24), 2341–2348. https://doi.org/10.1056/NEJMoa1614835

Lemon, L. S., Naimi, A., Caritis, S. N., Platt, R. W., Venkataramanan, R., & Bodnar, L. M. (2018). The role of preterm birth in the association between opioid maintenance therapy and neonatal abstinence syndrome. *Paediatric and Perinatal Epidemiology, 32*(2), 213–222. https://doi.org/10.1111/ppe.12443

Levran, O., Randesi, M., Li, Y., Rotrosen, J., Ott, J., Adelson, M., & Kreek, M. J. (2014). Drug addiction and stress-response genetic variability: Association study in African Americans. *Annals of Human Genetics, 78*(4), 290–298. https://doi.org/10.1111/ahg.12064

Liu, T., Lewis, T., Gauda, E., Gobburu, J., & Ivaturi, V. (2016). Mechanistic population pharmacokinetics of morphine in newborns with abstinence syndrome after oral administration of diluted tincture of opium. *Journal of Clinical Pharmacology, 56*(8), 1009–1018. https://doi.org/10.1002/jcph.696

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLOS Medicine, 6*(7), Article e1000097. https://doi.org/10.1371/journal.pmed.1000097

Monnelly, V. J., Hamilton, R., Chappell, F. M., Mactier, H., & Boardman, J. P. (2019). Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: A systematic review and meta-analysis. *Developmental Medicine & Child Neurology, 61*(7), 750–760. https://doi.org/10.1111/dmcn.14117

Moons, W. G., Way, B. M., & Taylor, S. E. (2014). Oxytocin and vasopressin receptor polymorphisms interact with circulating neuropeptides to predict human emotional reactions to stress. *Emotion, 14*(3), 562–572. https://doi.org/10.1037/a0035503

Moore, J. N., Gastonguay, M. R., Ng, C. M., Adeniyi-Jones, S. C., Moody, D. E., Fang, W. B., & Kraft, W. K. (2018). The pharmacokinetics and pharmacodynamics of buprenorphine in neonatal abstinence syndrome. *Clinical Pharmacology and Therapeutics, 103*(6), 1029–1037. https://doi.org/10.1002/cpt.1064

Ng, C. M., Dombrowsky, E., Lin, H., Erlich, M. E., Moody, D. E., Barrett, J. S., & Kraft, W. K. (2015). Population pharmacokinetic model of sublingual buprenorphine in neonatal abstinence syndrome. *Pharmacotherapy, 35*(7), 670–680. https://doi.org/10.1002/phar.1610

Oji-Mmuo, C. N., Michael, E. J., McLatchy, J., Lewis, M. M., Becker, J. E., & Doheny, K. K. (2016). Skin conductance at baseline and postheel lance reflects sympathetic activation in neonatal opiate withdrawal. *Acta Paediatrica, 105*(3), e99–e106. https://doi.org/10.1111/apa.13287

Parlaman, J., Deodhar, P., Sanders, V., Jerome, J., & McDaniel, C. (2019). Improving care for infants with neonatal abstinence syndrome: A multi-center, community hospital-based study. *Hospital Pediatrics, 9*(8), 608–614. https://doi.org/10.1542/hpeds.2019-0083

Patrick, S. W., Davis, M. M., Lehmann, C. U., & Cooper, W. O. (2015, August). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *Journal of Perinatolgy, 35*(8), 650–655. https://doi.org/10.1038/jp.2015.36

Schubach, N. E., Meler, K., Roth, B., Korsch, E., Laux, R., Singer, D., & Hünseler, C. (2016). Skin conductance in newborns suffering from abstinence syndrome and unexposed newborns. *European Journal of Pediatrics, 175*(6), 859–868. https://doi.org/10.1007/s00431-016-2716-8

Timpson, W., Killoran, C., Maranda, L., Picarillo, A., & Bloch-Salisbury, E. (2018). A quality improvement initiative to increase scoring consistency and accuracy of the Finnegan tool: Challenges in obtaining reliable assessments of drug withdrawal in neonatal abstinence syndrome. *Advances in Neonatal Care, 18*(1), 70–78. https://doi.org/10.1097/ANC.0000000000000441

Tolia, V. N., Murthy, K., Bennett, M. M., Miller, E. S., Benjamin, D. K., Smith, P. B., & Clark, R. H. (2018, January 1). Antenatal methadone vs buprenorphine exposure and length of hospital stay in newborns admitted to the intensive care unit with neonatal abstinence syndrome. *Journal of Perinatology, 38*(1), 75–79. https://doi.org/10.1038/jp.2017.157

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007, October 20). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *The Lancet, 370*(9596), 1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X

Wachman, E. M., Grossman, M., Schiff, D. M., Philipp, B. L., Minear, S., Hutton, E., & Whalen, B. L. (2018, May 8). Quality improvement initiative to improve inpatient outcomes for neonatal abstinence syndrome. *Journal of Perinatology, 38*(8), 1114–1122. https://doi.org/10.1038/s41372-018-0109-8

Wachman, E. M., Hayes, M. J., Brown, M. S., Paul, J., Harvey-Wilkes, K., Terrin, N., & Davis, J. M. (2013). Association of *OPRM1* and *COMT* single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *JAMA, 309*(17), 1821–1827. https://doi.org/10.1001/jama.2013.3411

Wachman, E. M., Hayes, M. J., Sherva, R., Brown, M. S., Davis, J. M., Farrer, L. A., & Nielsen, D. A. (2015). Variations in opioid receptor genes in neonatal abstinence syndrome. *Drug and Alcohol Dependence, 155*, 253–259. https://doi.org/10.1016/j.drugalcdep.2015.07.001 Q12

Wachman, E. M., Hayes, M. J., Shrestha, H., Nikita, F. N. U., Nolin, A., Hoyo, L., & Nielsen, D. A. (2018, March 25). Epigenetic variation in *OPRM1* gene in opioid-exposed mother-infant dyads. *Genes, Brain and Behavior, 17*(7). . Article e12476. https://doi.org/10.1111/gbb.12476

Wachman, E. M., Saia, K., Miller, M., Valle, E., Shrestha, H., Carter, G., & Jones, H. (2019). Naltrexone treatment for pregnant women with opioid use disorder compared with matched buprenorphine control subjects. *Clinical Therapeutics, 41*(9), 1681–1689. https://doi.org/10.1016/j.clinthera.2019.07.003

Whittemore, R., & Knafl, K. (2005). The integrative review: Updated methodology. *Journal of Advanced Nursing, 52*(5), 546–553. https://doi.org/10.1111/j.1365-2648.2005.03621.x

Wiles, J. R., Isemann, B., Mizuno, T., Tabangin, M. E., Ward, L. P., Akinbi, H., & Vinks, A. A. (2015). Pharmacokinetics of oral methadone in the treatment of neonatal abstinence syndrome: A pilot study. *Journal of Pediatrics, 167*(6), 1214–1220. https://doi.org/10.1016/j.jpeds.2015.08.032

Supplemental Material

Note: To access the supplemental material that accompanies this article, visit the online version of the *Journal of Obstetric, Gynecologic, & Neonatal Nursing* at http://jognn.org and at https://doi.org/10.1016/j.jogn.2021.04.014.