Neonatal Abstinence Syndrome

Review of Epidemiology, Care Models, and Current Understanding of Outcomes

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KEYWORDS

- Neonatal abstinence syndrome (NAS)
- Neonatal opioid withdrawal syndrome (NOWS) • Opioid exposed newborn (OEN)
- Prenatal substance exposure • Eat sleep console (ESC) • Pharmacotherapy
- Length of stay (LOS) • Developmental outcomes

KEY POINTS

- Multiple individual and demographic factors contribute to neonatal abstinence syndrome severity and clinical course.
- Emerging evidence supports the importance of parental roles in care.
- Studies support evolving care models to focus on nonpharmacologic treatment and family-centered care.
- Long-term outcomes from neonatal abstinence syndrome are poorly understood and must be considered in context of multiple individual, familial, and societal factors.

BACKGROUND

Neonatal abstinence syndrome (NAS) includes an array of symptoms impacting opioid-exposed newborns (OEN) owing to postnatal withdrawal from in utero substance exposure. More recently, the term neonatal opioid withdrawal syndrome has emerged to specify prenatal opioid exposure, but NAS remains the dominant term in the literature. NAS symptoms generally occur in the first 24 hours of life for short-acting opioid exposure and within 72 to 96 hours of life for long-acting

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opioid exposure. The most frequently reported symptoms include tremors, restlessness, hyperactive reflexes, regurgitation, increased tone, high-pitched cry, frantic suck, and difficulty sleeping.[1–3] OEN have lengthy hospital stays, higher costs, and in some settings, separation from their mothers, during the newborn hospitalization.[4–7] NAS can impact an infant's ability to grow and thrive and contribute to caregiver distress.[8,9] Emerging evidence supports the importance of environment of care and parental engagement in NAS care, mitigating symptoms, improving outcomes, and supporting families.[10–12] This review summarizes current evidence on epidemiology and predictive factors, evolving assessment and treatment models, and the current understanding of postdischarge considerations and long-term outcomes.

EPIDEMIOLOGY AND PREDICTIVE FACTORS

With the expansion of the opioid epidemic in the United States, prenatal exposure to both illicit and prescribed opioids and subsequent incidence of NAS has also increased dramatically.[4,13–16] A recent study based on the National Inpatient Sample, a representative sample of US hospital discharges, found that from 2000 to 2014, incidence of NAS in the United States has increased 5-fold, from 1.5 to 8.0 per 1000 hospital births.[4] In the United States, NAS has disproportionately impacted rural and public health insurance–dependent populations, with both rates of NAS and associated hospital costs growing at a faster pace compared with urban and privately insured peers. Rural families impacted by NAS are more likely than their urban peers to have a lower family income and be dependent on health insurance.[16] Those insured by Medicaid are more likely to have longer hospital stays and to require transfer to other hospitals for NAS management,[4] potentially creating new burdens and barriers for families. A recent single-site, prospective cohort study found that maternal food insecurity is correlated with an increased likelihood for the need for pharmacologic treatment of NAS in their infants. This association was independent of maternal depression or type of opioid agonist medication-assisted treatment (MAT) prescribed to mothers.[17]

NAS risk seems to be associated with several demographic factors. Based on national data compiled by the Agency for Healthcare Research and Quality, NAS rates are higher among non-Hispanic white infants, with more than 10 per 1000 births compared with fewer than 3 per 1000 births among infants of other races/ethnicities in the United Stgates.[18] In a retrospective cohort study of infants enrolled in Medicaid in Tennessee, male sex was associated with increased likelihood of NAS requiring pharmacologic treatment, independent of multiple maternal factors including age, race, and education, anxiety, or depression; in utero exposures to selective serotonin reuptake inhibitors or cigarettes; opioid type or dosing; and infant birth weight or small for gestation age.[19] However, prior studies have shown conflicting results regarding whether there was an effect of gender on symptom severity or likelihood to need treatment independent of maternal and neonatal factors.[20–22]

Coexposure to other psychotropic medication, including selective serotonin reuptake inhibitors, benzodiazepines, and other illicit substances increases the risk of significant withdrawal symptoms.[2,7,23] Genetic and epigenetic factors also seem to influence the clinical course of NAS. Studies have identified variation in genotype and epigenetic markers related to mu-opioid receptors, modulators of pain sensitivity, dopamine metabolism, and stress pathways as important to variation NAS symptom severity, response to opioid medications in the neonatal period, and clinical outcomes such as hospital length of stay (LOS).[24–26] Ongoing

exploration of genetic and epigenetic markers may further elucidate individual variation in response to pharmacotherapy and development of clinical prediction models.

VARIATION IN INPATIENT CARE

There is wide variability in the inpatient care and costs for NAS.[5,27–29] Standardizing hospital policies and care processes for NAS is recommended by the American Academy of Pediatrics and has been shown to improve hospital care and outcomes.[2,15] A survey of policies and practices in hospitals participating in the Better Outcomes Through Research For Newborns (BORN) network in 2015 found that the majority of responding hospitals had NAS management protocols. Of these, 72% addressed pharmacologic treatment, although only 58% addressed nonpharmacologic supportive care. Observation periods for OENs varied: for short-acting opioids, 57% observed for 2 to 3 days and 30% for 5 or more days. For long-acting opioids 71% observed for 4 to 5 days, 8% observed for 7 or more days, and 19% observed for only 2 to 3 days. A majority of hospitals observed for NAS in level 1 nurseries, but of these most (87%) transferred to neonatal intensive care unit (NICU) settings when starting pharmacotherapy.[27] Similarly, a study of infants with NAS discharged from children's hospitals in the Pediatric Health Information System found 93% of newborns receiving pharmacotherapy were admitted to the NICU, although individual hospital rates varied from 0% to 100%. Rates of pharmacotherapy were high overall, with 70% of newborns with NAS treated pharmacologically and pharmacotherapy rates by hospital ranging from 13% to 90%. Consistent with findings in earlier studies, pharmacotherapy was linked to a more than 2-fold increase in LOS (22.0 vs 10.9 days) and total hospital costs ($44,720 vs $20,708) compared with newborns with NAS not treated pharmacologically.[28]

CHOICE OF PHARMACOLOGIC AGENT

When pharmacotherapy for NAS is indicated, an opioid agonist is often selected as first line. In the BORN network survey, morphine was the most common first-line pharmacologic agent used by participating hospitals, followed by methadone.[27] A review of NAS hospitalizations in the Pediatric Health Information System records also found morphine to be the most common pharmacotherapy choice for NAS, received by 90% of pharmacologically treated newborns, whereas 13% received methadone. Phenobarbital was the adjunctive agent of choice, with 20% of treated newborns receiving both morphine and phenobarbital.[28]

A large retrospective review using 2011 to 2015 data from the Pediatrix Clinical Data Warehouse compared outcomes among newborns treated with either morphine or methadone in the first week of life. The majority (85%) received morphine; however, those who received methadone as first-line pharmacotherapy had a 22% decrease in average hospital LOS, spent less time in the NICU, and were less likely to require an adjunctive agent.[30] A recent multicenter, randomized, controlled trial comparing methadone with morphine in NAS patients pharmacologically treated in 2014 to 2017 found a 14% decrease in mean hospital LOS and a 16% decrease in opioid treatment days in the methadone group.[31] Earlier smaller studies comparing morphine and methadone have shown conflicting results. A single-center, randomized trial found newborns with NAS treated with methadone rather than morphine had fewer opioid treatment days,[32] and a retrospective cohort study found fewer opioid treatment days to be associated with morphine compared with methadone.[33] Buprenorphine has also been proposed as an alternative opioid

agonist therapy for NAS and several small studies have found a shorter duration of treatment and shorter hospital LOS with buprenorphine compared with either methadone or morphine.[34–36] Overall, these findings seem to favor longer acting opioid agonists over shorter acting agents.

A second pharmacologic agent is often added when a newborn with NAS has symptoms that are difficult to control with opioid agonist treatment or is having difficulty weaning their dose. A second agent may be particularly useful in cases of prenatal polypharmacy, including exposure to selective serotonin reuptake inhibitors and benzodiazepines in addition to opioids.[37–40] Phenobarbital is most frequently used[27,28]; however, concerns have been raised about impact on the developing brain with potential impact on behavioral and cognitive outcomes.[41–43] Studies have showed mixed benefits of clonidine as an alternative second agent. A single-center, prospective, nonblinded, block randomized trial found that adjunctive treatment with phenobarbital rather than clonidine led to a lesser average number of days of morphine treatment, but no difference in total morphine dose and longer total pharmacologic treatment duration, with phenobarbital continued for a mean of 3.8 months after discharge. There was no significant difference in adverse events or treatment failures.[38] Conversely, a retrospective study of adjunctive treatment with clonidine versus phenobarbital found the clonidine group had 8.5 days shorter mean opioid treatment duration.[39]

PHARMACOTHERAPY DOSING

Structured protocols for pharmacotherapy initiation and weaning have been associated with improved NAS outcomes.[15,44] Conventionally, once pharmacotherapy is initiated, it is titrated until symptoms are considered captured below the treatment threshold and then weaned off slowly, typically by 10% of the peak dose once or twice daily when symptoms remain below the threshold; the infant is discharged only after a period of observation off pharmacotherapy.[2,3,6] This practice contributes to lengthy hospital stays and there is no evidence base to support the necessity of slow weans or prolonged pharmacotherapy courses.[15,44] Alternative dosing approaches are emerging in the literature.[6,40,45–52] One single-center retrospective cohort report found a decreased LOS and decreased cumulative morphine using a structured weight-based weaning protocol compared with a symptom-based weaning protocol.[45] Multiple studies comparing outpatient weaning of opioid pharmacotherapy versus inpatient weaning have demonstrated shorted hospital LOS and decreased hospital costs without increased hospital readmission. However, there were mixed findings regarding the total duration of opioid treatment[46–51] and 1 study found increased post-discharge emergency department use in the outpatient treatment group.[48] Several institutions have moved to using single as-needed doses of morphine or methadone as opposed to the typical titration and weaning course as part of larger quality improvement initiatives.[6,52] One published report demonstrated that, when combined with optimized nonpharmacologic treatment as the first line of NAS care, the number of doses and cumulative amount of opioid therapy can be substantially and safely decreased.[52]

EVOLVING CARE MODELS

MAT, typically with the opioid agonists methadone or buprenorphine, is the currently recommended management for opioid use disorders in pregnancy to prevent risks associated with withdrawal during pregnancy in mothers. This has contributed to overall increased rates of NAS and altered the landscape of prenatal opioid exposure,

with more infants exposed prenatally to daily opioid-mediated treatment.[3,4,53–55] This has impacted the family structures, home environments, and resources of infants with NAS, with a greater proportion of birth mothers actively in recovery and often better equipped to participate in their newborn's care both in the hospital and at home. There is an evolving frameshift in the literature around NAS care, with a greater emphasis on the mother–child dyad and family-centered care. The most recent American Academy of Pediatrics Clinical Report on Neonatal Drug Withdrawal states that, "the goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment" and recognizes nonpharmacologic care as the first line in NAS treatment, including optimizing the environment of the infant, minimizing overstimulation and hunger, and providing a variety of soothing supports.[2] Suggested nonpharmacologic interventions may include soothing techniques that mimic the womb such as swaddling, holding and swaying motions, skin-to-skin contact, providing a low-stimulation environment, careful attention to feeding cues, on-demand feeding and provision of sufficient calories, encouraging mother–infant bonding, and creating supportive environments for families.[6,8,11,56,57]

NONPHARMACOLOGIC CARE

At many institutions, OENs are monitored in a NICU where infants are separated from their mothers. In some institutions, this separation occurs only once pharmacotherapy is initiated for those who need it, whereas in others, this practice is in place during observation for withdrawal symptoms.[27–29] However, the NICU environment may not be an ideal setting for these withdrawing newborns, who may already have difficulty with state regulation and may be especially sensitive to the noise, bright lights, and high activity levels in NICU.[8,58] Rooming-in environments, where mother and child stay together 24 hours a day unless separation is indicated for medical or safety reasons, is the World Health Organization recommended standard of care for newborns.[59] Rooming-in may be an important factor in optimizing nonpharmacologic care for the OEN. It has been shown in multiple single-center studies,[52,60–64] as well as a recent systematic review and meta-analysis,[12] to improve NAS hospitalization outcomes, decrease rates of pharmacotherapy, and shorten hospital LOS, without any reported increase in adverse events. A policy of separation of mothers from their infants during NAS hospitalization may interfere with bonding and contribute to maternal perceptions of stigma.[8,9,65] Additionally, a recent study demonstrated a positive correlation between amount of time mothers spend at the infants' bedside and improved NAS outcomes.[10]

FEEDING OPTIMIZATION AND BREASTFEEDING

Breastfeeding in mother–infant dyads with prescribed methadone or buprenorphine use is generally considered safe and beneficial to bonding and NAS symptoms management; however, there is wide variability in both breastfeeding rates, policies, and practices around breastfeeding in this population.[3,40,66–69] Among participating hospitals in the BORN network, 1 study found that 70% of hospitals had some policy or guideline in place regarding breastfeeding or feeding expressed breast milk to newborns being observed or treated for NAS. The criteria for breastfeeding eligibility was variable, with 50% requiring negative drug screening at delivery and 40% requiring enrollment in a substance use disorder treatment program.[27] Mothers may also face significant psychosocial and economic barriers to breastfeeding while receiving MAT.[69,70] Studies have shown lower rates of breastfeeding among infants

with NAS than comparison groups. However, among eligible mother–infant dyads, rates of breastfeeding may be improved with integrated models of care for the mother and the infant.[66,68] Multiple studies have now linked breastfeeding with improved NAS hospital outcomes, including decreased hospital LOS and decreased pharmacotherapy.[66,71–74] Although these findings have not controlled for rooming-in, increased holding or other associated nonpharmacologic care, the potential benefit of increased maternal presence and engagement seems clear.

Standardizing nonpharmacologic and pharmacologic treatment holds promise for improving hospital care and experiences and can be implemented successfully on larger scales. One multicenter collaborative through the Vermont Oxford Network QI demonstrated improved outcomes, including decreased LOS and decreased pharmacotherapy, in participating hospitals through the adoption of a toolkit that addressed standardization of NAS identification, assessment, and management; standardization of processes for reporting and measuring NAS rates and outcomes; and focusing on creating environments that better supported the mother–child dyad, including instruction in trauma-informed care.[15]

ASSESSMENT MODELS

The Finnegan Neonatal Abstinence Scoring System (FNASS) and its variants have been the dominant models for assessment and management of NAS since it was first published in 1975.[1,27,75] Of hospitals participating in the BORN network, 92% reported using a version of the Finnegan Scale, with 70% using the Modified Finnegan Scale and 22% the Original Finnegan Scale.[27]

The FNASS has considerable limitations, including a lengthy symptom catalog, some of which have unclear clinical significance, and the assessment of which requires disturbing the infant and potentially exacerbating observed symptoms.[75] One analysis of the FNASS found poor internal psychometric properties and internal consistency guiding peak scores and pharmacotherapy initiation.[76] There is a lack of evidence supporting commonly used cut-offs guiding management, with most institutional FNASS based protocols starting or increasing pharmacologic treatment after an infant has received 3 scores of 8 or greater or 2 scores of 12 or greater.[6] This approach has never been validated and it is unclear how to differentiate fluctuations in FNASS score related to withdrawal versus variation in typical infant behaviors.[6,75,77] A study of infants without in utero substance exposure found that, although the FNASS scores were rarely greater than 7 in the first 3 days of life, scores increased with age and by 5 to 6 weeks of age, the 95th percentile cut-off score was as high as 8 with significant variations between day and night.[78]

Largely in response to these limitations, the Eat, Sleep, Console (ESC) approach was developed by Grossman and colleagues[52,75,77] as a foundation for functional clinical assessments of NAS guiding management. Infants are assessed based on their ability to successfully breastfeed or take a sufficient volume of expressed breastmilk or formula at each feed, sleep without interruption for at least 1 hour, and be consoled by caregivers within 10 minutes when fussing. If the infant is unable to meet these goals, multidisciplinary team huddles are called to optimize nonpharmacologic care first and consider pharmacologic management. This approach allows for frequent clinical assessments without disturbing the infant outside of routine care and encourages in-time responses that prioritize nonpharmacologic care. The investigators at Yale concurrently continued FNASS scoring and were able to compare outcomes with ESC management versus predicted outcomes using the Finnegan approach for a subset of OENs. The reported proportion of infants treated with morphine using the ESC

approach was 12% compared with an estimated 62% predicted using the FNASS approach and average LOS for using the ESC tool was 5.9 days compared with an estimated average 16 days using FNASS.[77] Other institutions are adopting the ESC approach, largely as part of quality improvement initiatives and report substantial decreases in LOS and need for pharmacotherapy when used in combination with other measures supporting nonpharmacologic care.[75,79,80]

READMISSION AND HEALTH CARE USE

After the initial birth hospitalization, children with history of NAS have more frequent interactions with the health care system outside of routine health maintenance visits in the future. A longitudinal retrospective cohort study using data from the New York State Inpatient Database from 2006 to 2009 showed infants with a history of NAS had higher 30-day and 1-year readmission rates than infants born at term without NAS; readmission rates were similar to those of late preterm infants.[81] Conversely, a study using Pediatric Health Information System data found that term newborns with NAS had lower readmission rates than those without NAS at both 30 and 90 days compared with newborns without NAS, with no difference in hospital mortality.[28] An Australian population-based study linking hospital, birth, and death records found increased rates of hospitalization throughout childhood, persisting into adolescence. In childhood, NAS history was a predictor of admission for maltreatment and mental and behavioral disorders.[82] A retrospective longitudinal cohort study using linked claims data including inpatient, emergency department, and outpatient care found that children ages 1 to 8 years with a history of NAS had a significantly greater number of claims per year with nearly double mean annualized costs for all health services. Although costs and claims were steady or decreasing for other children after age 3, they progressively increased for children with a history of NAS. Additionally, well-child and preventive visits accounted for a significantly smaller proportion of encounter codes for children with NAS.[83] This finding reflects increased vulnerability among children with NAS and their families, not only increased health needs, but likely also social and economic needs impacting the way they navigate the health care system.

GROWTH AND NUTRITION

Infants with NAS are at risk for failure to thrive. Prenatal opioid exposure is associated with small for gestational age size at birth; in the neonatal period, this population often experiences poor feeding coordination and hyperphagia owing to increased metabolic needs.[1–3] Careful monitoring of feeding and growth is an important aspect of NAS care. Caloric fortification of formula and breastmilk may be initiated when there are signs of excessive early weight loss or failure to gain weight.[2,3] Survey of the BORN network found that one-third of responding hospitals provided caloric enhancement to all infants observed or treated for NAS.[27] A recent single-center study randomized newborns with prenatal methadone exposure to receive either standard (20 kcal/oz) or fortified (24 kcal/oz) formula and found similar days to weight nadir and percent maximum early weight loss, but a longitudinal analysis revealed a higher percent weight gained per day in the higher calorie group at 21 days, suggesting a potential benefit for early caloric fortification.[84]

Specific, longer term nutritional needs of this population remain uncertain. A retrospective of 70 term, singleton infants with NAS and controls matched for gestational age, birth weight, gender and insurance type at a tertiary center with level IV NICU followed growth over the first 400 days of life found both groups had similar growth

curves. Interestingly, wider 10th and 90th percentile growth curves were seen for infants with NAS, although this finding did not attain statistical significance.[85] These findings may suggest a varied course in which some babies with NAS continue to struggle with growth after discharge, whereas others may be overfed in response to either hyperphagia, misinterpretation of feeding cues, or efforts to soothe fussy but fed infants. A further exploration of growth and feeding patterns in infancy and childhood for this population is needed.

BRAIN DEVELOPMENT

Several studies have demonstrated changes in the human brain in response to opioid exposure in adult humans, altering gray matter volume[86,87] as well changes in brain and cerebellar size and content in animal studies.[88–92] More recently, studies have demonstrated similar alteration in newborns with NAS.

A recent large prospective study of late preterm and term newborns found that those newborns with prenatal opioid exposure requiring pharmacologic treatment for NAS were more likely to have small head circumference (at or below both 3rd and 10th percentile curves) than controls without prenatal opioid or illicit substance exposure matched on gestational age, mode of delivery, race and maternal parity. The majority of mothers in the sample were receiving MAT and the relative reduction in head circumference seems to be independent of other substance coexposures.[93] Notably, those newborns with NAS not requiring pharmacologic treatment were excluded from results and there may other factors at play in the relationship between brain growth and withdrawal symptoms. Several earlier, smaller studies using MRIs of the brain have also found decreases in infant head circumference and whole brain volume and findings, suggesting that certain brain regions, including the basal ganglia, thalamus, and white matter tracts, may be particularly affected by prenatal opioid exposure.[94–97] These findings of altered brain volume and morphology seem to persist in childhood through school age,[97–100] but the functional significance of these findings as well as causal relationships with other prenatal and childhood stressors remain unclear.

COGNITIVE AND BEHAVIORAL OUTCOMES

Several studies have demonstrated an association of NAS with cognitive and developmental delay in preschool and grade school aged children.[101–107] In a recent study linking Tennessee Medicaid and Birth Certificate data with Tennessee State Department of Education special education data for those born between 2008 and 2011, ages 3 to 8 at the time of sampling, children with a history of NAS were more likely to have a referral made for evaluation of an educational disability, to meet criteria for either developmental delay or speech and language impairment, and also to receive services or therapies for these diagnoses than peers without history of NAS matched by age, gender, ethnicity, and Medicaid enrollment status.[103]

An Australian study linking health data and educational testing data from the National Assessment Program: Literacy and Numeracy examinations found that children with a history of NAS had significantly lower mean composite test scores and were more likely not to meet minimum standards at grades 3, 5, and 7 than peers matched for gender, gestational age at birth, and socioeconomic status. Older maternal age and higher level of maternal education seemed to be protective against failure to meet educational standards.[104]

Prenatal opioid exposure has also been linked to increased rates of attention deficit hyperactivity disorder, behavioral problems, and executive function issues.[108–113]

However, there are multiple factors that may impact these findings. In studies of children with prenatal heroin exposure, outcomes including findings of increased attention deficit hyperactivity disorder, inattention and aggressions, and lower performance on measures of intelligence were mitigated by home environment, adoption, and socioeconomic status.[102,109,114]

In a study of mother–child pairs with prenatal MAT, either methadone or buprenorphine, those in the MAT group had lower scores in measures of both cognitive development and mother–child interactions, but higher quality mother–child interactions positively impacted narrative memory and vocabulary scores across groups.[107] Additionally, recently published results from the MOTHER trial showed no difference in developmental outcomes between infants of mothers prenatally prescribed methadone and buprenorphine exposure and that children from both subsets were following normal tracks for physical growth and cognitive and language development. Mother–child pairs in this sample generally scored well in a measure of home environment.[115]

Early intervention services may be beneficial in mitigating the observed, likely multifactorial, impact of NAS on developmental, cognitive, and behavioral outcomes; this area deserves further exploration.[106,116,117] Despite being eligible, many children do not go on to receive early intervention services. A recent retrospective cohort study found less than one-half of infants with NAS eligible for early intervention services at time of discharge were subsequently enrolled. Those discharged home with a biological parent were more likely to be referred and those with longer hospital stays more likely to enroll, highlighting potential gaps in outpatient care for those discharged early or into nonparental care.[116]

SUMMARY AND FUTURE DIRECTIONS

Most studies of NAS outcomes have focused on linear causal relationships; however, as recently highlighted by Kaltenbach and colleagues,[115] there likely is no single cause to findings of longer term developmental and educational differences in children with prenatal opioid exposure, necessitating a shift in conceptual framework. The functional outcomes for this population likely reflect a complex interplay of genetic and epigenetic factors, prenatal and childhood stressors, and mitigating factors. More recent successful interventions in this population have addressed environmental and social factors and shifted focus to the mother–child dyad. It is worth noting that a majority of substance exposed infants have some involvement of child welfare services and many infants with NAS do not go home in the custody of their biological mothers.[15,118] Support is essential for these infants and their caregivers during the birth hospitalization, discharge to home, and early childhood. Future research on long-term outcomes is needed with careful planning to account for environmental factors and recognition of the role of family and community dynamics, in addition to individual variables, to understand causal relationships and better direct potential interventions at both the individual and policy levels.

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