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# Care of the Infant With Neonatal Abstinence Syndrome

## *Strength of the Evidence*

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## ABSTRACT

There is little empirical evidence that guides management of infants with neonatal abstinence syndrome. The standard of care first described in the 1970s is still prevalent today, although it has never been tested in this population. Standard of care interventions include decreasing external stimulation, holding, nonnutritive sucking, swaddling, pressure/rubbing, and rocking. These interventions meet the goals of nonpharmacologic interventions, which are to facilitate parental attachment and decrease external stimuli. Many nursing interventions used in infants with neonatal abstinence syndrome have been tested in low-birth-weight infants, whose treatment often includes the same goals. Those interventions include music therapy, kangaroo care, massage, and use of nonoscillating water beds. Nursing attitude has also been shown to be impactful on parental attachment. The American Academy of Pediatrics recommends breast-feeding in infants whose mothers are on methadone who do not have any other contraindication. It also provides guidelines for pharmacologic management but cannot provide specific recommendations about a standard first dose, escalation, or weaning schedule. Buprenorphine has some evidence about its safety in newborns with neonatal abstinence syndrome, but high-powered studies on its efficacy are currently lacking. There are many opportunities for both evidence-based projects and nursing research projects in this population.

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Neonatal abstinence syndrome (NAS) is one of the most challenging conditions faced by neonatal nurses today. Nursing management of NAS requires knowledge that has not been traditionally associated with neonatal intensive care unit (NICU), such as addiction behaviors, social risk factors, and psychosocial needs of parents with substance abuse problems. Attitudinal change may also be important when recognizing that opioids cause a chronic disorder in the addict brain, resulting in compulsive and uncontrollable drug craving, seeking, and use.[1,2] Nationally, the rates for NAS have more than tripled in the past decade, with 3.4 of every 1000 infants born with the syndrome.[3] In Florida, the rate was 4.4/1000 the same year (2009).[4] According to the 2011 National Survey on Drug Use and Health,[5] approximately 5% of pregnant women used illicit drugs, a rate that has not changed significantly since 2003. Although the rate of drug use remains similar, there is no sign of the problem abating. More than 3.1 million people used illicit drugs for the first time in 2011, just slightly higher than in 2010.[5] The purpose of this article was to update NICU nurses on the current best evidence that guides the nursing care of infants with NAS.

Methadone has been the gold standard for treating pregnant women who are addicted to opiates since 1995.[6] In fact, pregnant women in a methadone treatment program should be acknowledged for choosing a healthier path for themselves and their baby. On methadone, mothers are more likely to have prenatal care, more stable living conditions, improved nutrition, and deliver newborns with higher-birth-weights.[6,7] They participate in fewer high-risk social behaviors,

have fewer infectious diseases, and are less likely to overdose on illicit drugs.[6] The methadone dosing schedule is much safer for the fetus than unknown quantities of many different drugs.[6] Although some newborn infants exposed to methadone during pregnancy demonstrate no observable effects or withdrawal signs, most will exhibit signs of withdrawal after birth.[8–13] Historically, pharmacologic and nonpharmacologic interventions are based on the central nervous system and gastrointestinal, respiratory, and autonomic manifestations of neonatal withdrawal syndrome.[14,15]

## NONPHARMACOLOGIC INTERVENTIONS

The goals of nonpharmacologic interventions are to facilitate supportive parenting behaviors and manipulate (decrease) external stimuli that tend to exacerbate withdrawal signs. Velez and Jansson[16] asserted that a multilayered and comprehensive approach is crucial to nurture strong maternal-infant interactions in this population. They define nonpharmacologic care as "modification of the environment and social interactions that support neurodevelopmental and physiologic stability."(p113)

There are many options for nonpharmacologic interventions to decrease external stimuli and provide a soothing environment for the newborn described in the literature (see Tables 1 and 2), although none are well studied in the NAS population. Evidence gathered in studies from other neonatal populations, however, may be applied to infants with NAS within the scope of evidence-based practice. Dissemination of those outcomes will help build the evidence for nonpharmacologic management of these infants. Melnyk and Fineout-Overholt[17] provide a guide to review, critique, and apply evidence-based practice for nurses. One excellent example of applying evidence from the preterm infant population to those with NAS[18] had positive results. The author implemented skin-to-skin care for 1 hour after feedings in newborn infants with NAS to promote infant comfort and sleep, based on the neurobehavioral characteristics of preterm infants, and reported improvements in continuous quiet sleep.[18] The intervention not only enabled the infants to sleep better, the mothers felt good about their unique contribution to provide the intimate contact that comforted their infants exhibiting signs of withdrawal. Kangaroo care has been found to be safe and effective in many studies of low-birth-weight infants, with results including decreasing length of stay and improving measures of growth, breast-feeding, and maternal-infant bonding.[19] Although kangaroo care has not been specifically investigated in infants with NAS, evidence from studies on low-birth-weight infants may support the use of kangaroo care in less vulnerable populations, such as those with NAS, through an evidence-based practice project.

The NICU environment itself can be a source of stress for infants with NAS. Although there is no scientific evidence that turning the lights down, talking quietly, and sequestering the infant in a private room whenever possible decrease sleep disturbances, it makes sense to include these simple nonpharmacological interventions in care to reduce environmental stimuli and enhance comfort. Sometimes, however, the only possible bed placement is in a brightly lit room with many other infants. In that case, the best option is to find the quietest area and avoid noisy ventilators or newly admitted infants who demand lots of attention from many clinicians. If policy permits, a blanket can be draped across the crib to shield light from the infant's eyes. Some NICUs are dedicating space to the NAS population in an effort to cohort infants together. Keeping infants with NAS in a room together or in adjacent spaces facilitates development of the nursing skill set that can directly impact neonatal outcomes. Although these infants do not require the highly advanced technical skills required by the typical NICU patient, they can be very demanding. Clinical sign and symptom assessments are based on the quality of nursing surveillance, which is difficult for nurses to do when also caring for a critically ill neonate. Nurses can also be "cohorted" to care for these infants and their parents. Their assessment skills are honed in a different way, and they can establish high levels of interrater reliability in the withdrawal assessment scale, as well as gain expertise in working with parents with such specific needs. Any additional potential stressors should be critically evaluated before subjecting the infant recovering from physical dependence, such as elective circumcision, and, ideally should not be scheduled until the infant is fully recovered, perhaps even after discharge from the NICU.

Infant massage is an intervention often provided by a licensed massage therapist or mothers who have been trained by a massage therapist. Again, there are no published studies of the impact of massage on infants with NAS, but it has been studied in other vulnerable neonatal populations.[20–22] Outcomes in very low-birth-weight infants included better weight gain,[20] significantly decreased stress behaviors ($P < .05$),[21] and significantly better neurodevelopmental outcomes at 2 years of age.[22] Preterm infants in these studies were massaged for 15 minutes 3 to 4 times a day (see Table 1).

Another "intervention" that exists in some NICUs for infants with NAS is music therapy. Although not studied in infants with NAS, nurses have either adapted the practice or allowed mothers to implement it. One study by Loewy and colleagues[23] compared mothers singing

Table 1. **Nonpharmacologic interventions: characteristics of selected publications with potentially helpful interventions supported by empirical evidence and 1 evidence-based practice project in various neonatal populations**

| Citation | Intervention | Population | Design/measures | Pertinent Results[a] |
|---|---|---|---|---|
| Field et al (2008)[24] | Aroma therapy (lavender oil) using bath water as vehicle | 30 term normal infants; 1-14 wk old | RCT/bath and sleep behaviors; salivary cortisol | Infants with aroma therapy slept more ($P < .05$) and cried less ($P < .05$) than others; cortisol decreased in aroma therapy in mothers ($P < .005$) and in infants ($P < .05$) |
| Conde-Agudelo et al (2011)[19] | Kangaroo care | 2518 LBW infants | Meta-analysis of 16 RCT/various measures | Not harmful in LBW infants; increased some measures of infant growth, breast-feeding, and maternal-infant attachment |
| Hiles (2011)[18] | Kangaroo care | NAS (number not specified) | EBP project/KC for 1 h postfeeding | Infants slept longer with KC; mothers felt positive about their contribution |
| Ang et al (2012)[20] | 15-min massages (×3) per day (or sham) M-F for 4 wk or discharge | 120 infants, 28- to 33-wk gestation | Blinded RCT/immune system markers | Massage well tolerated; no adverse events related to massage; better weight gain in massage group |
| Hernandez-Reif et al (2007)[21] | 15-min massages (×3) per day for 5 d | 36 infants, 28- to 32-wk gestation | RCT/stress behaviors measured during first massage and last massage | Massage group had significant decrease in stress behaviors over time ($P < .05$) |
| Procianoy et al (2010)[22] | 15-min massages (×4) per day by mothers | 73 infants, 750-1500 g | RCT/massage + KC vs KC alone | Massaged infants had significantly better neurodeveloped outcomes at 2 y (MDI and PDI) |
| Loewy et al (2013)[23] | Music therapy | 272 infants >31 wk in 3 NICUs | RCT, multisite/VS, activity level | Live sung lullaby by mother improved HR, sucking, and feeding behaviors, and ocean disc induced quiet-alert states and $O_2$ sat improvements |
| Oro and Dixon (1988)[25] | Water beds | 30 infants with NAS | RCT/medication use, weight gain | Waterbed group used less medication to control symptoms; earlier weight gain |

Abbreviations: EBP, evidence-based practice; HR, heart rate; KC, Kangaroo care; LBW, low-birth-weight; MDI, Normal Mental Developmental Index; M-F, Monday through Friday; NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit; PDI, Psychomotor Developmental Index; RCT, randomized controlled trial; VS, vital signs.

[a]Pertinent results are those that may have implications for infants with NAS. Not all study results are included in this summary.

a lullaby (culturally based or "twinkle twinkle") against sounds that resemble fluid sounds of the womb and others that resembled the intrauterine heartbeat. They tested the differences in vital signs, activity, and oxygen levels in 272 infants older than 31 weeks of gestation in 3 NICUs. The researchers reported that mother's singing significantly improved the heart rate, sucking, and feeding behaviors, while the womb sounds induced quiet-alert states and improvement in oxygen saturations. Soft singing might be helpful to both infants with NAS and their mothers, but there is no evidence to support it as an intervention.

Table 2. **Nonpharmacologic interventions: characteristics of potentially helpful interventions for infants with NAS supported by expert opinion only[16]**

| Intervention | Purpose/use |
|---|---|
| Decreased environmental stimuli | Room should be quiet, dimly lit, and use slow infant handling |
| Frequent small/demand feedings | May help in infants with motor or tone dysregulation |
| Holding | Infants who have poor motor control (thrashing or exaggerated rooting) respond to gentle head/limb restraint by helping them regulate |
| Nonnutritive sucking | Helps organize a dysregulated infant and prevents disorganization |
| Swaddling | Helps maintain regulation, self-soothe, and better tolerate stimulation (such as diaper change) |
| Containment | Gentle containment or pressure supports motor and tone control |
| Rubbing | Rubbing often better than patting when burping during feedings to avoid triggering Moro reflex |
| Vertical rocking | Facilitates relaxation and eye contact; more soothing than "regular" rocking or side to side. |

Two randomized controlled trials were found that tested nonpharmacological interventions in infants with NAS, both older studies. The study by Oro and Dixon[25] tested the effect of a nonoscillating water bed against a standard mattress in 30 infants with NAS. They reported that the infants in the waterbeds used less medication to control withdrawal signs and demonstrated earlier consistent weight gain. It is never advised to adopt interventions on the basis of a single study, however, because interventions must be replicated in other settings to confirm the efficacy and effectiveness. This would be an easy and cost-effective evidence-based practice project in a NICU that already has at least 1 nonoscillating water bed. Another randomized controlled trial in a smaller population of 14 infants with NAS demonstrated that mechanical rocking beds produced significantly higher NAS scores ($P = .05$) and more sleep disruption ($P = .01$) in infants with NAS and, therefore, is not recommended in this population without further study.[26] Although positive results are most often expected and reported, it is extremely helpful to know what interventions are not helpful so that they can be abandoned or studied in a different manner. Another intervention that is known only by expert opinion to be unhelpful is eye contact,[16] especially when the infant is easily overstimulated. Once clinical signs of withdrawal are under control and the infant is recovering, eye contact is more easily tolerated. Of course, eye contact is very important for maternal-infant bonding, so mothers of infants with NAS must be taught to interpret their infants' cues and not force their own needs upon an infant who cannot look at them just yet.

There are several nonpharmacologic interventions that are commonly used but supported only by "expert opinion" rather than empirical evidence. Expert opinion is sometimes the only evidence available, especially when the interventions are standard care or informed common sense. It would be considered unethical to randomize commonly used NAS interventions to study the impact on patient outcomes, because it denies some infants the standard of care. Examples of untested interventions found in the literature include decreasing environmental stimuli, frequent small feedings, holding, swaddling, nonnutritive sucking, pressure/rubbing, and vertical rocking (see Table 2). Vertical rocking may not yet be a standard of care, but it seems to facilitate relaxation in infants with NAS and appears to be more soothing than horizontal rocking.[16] Similarly, rubbing an infants' back during burping can be less stimulating than patting, which tends to elicit a Moro reflex if the infant has increased central nervous system irritability.[16]

A final area that can be easily overlooked is the nurse's attitude and approach to caring for mothers of infants with NAS. It has long been established that NICU nurses tend to hold negative attitudes toward pregnant women who use illicit substances,[27–30] are judgmental,[29] and lack knowledge about substance abuse and its treatment.[30,31] Fraser and colleagues[32] identified findings such as these to be a barrier in promoting effective parent-child interaction. Several investigators, however, have studied the impact of education for nurses to improve their relationships with these families. Corse and colleagues[31] implemented a training program in a prenatal clinic to improve interviewing skills and client focus among nurse midwives. Their new interviewing style enabled a trusting relationship between the client and the midwife, which eventually impacted the midwives' attitudes toward their clients. Once their attitudes changed, the nurse midwives were much more successful in helping their clients to change their drug behaviors. Similarly, Gerace and colleagues[29] successfully provided workshops to improve nurses' knowledge in an effort to change attitudes toward patients with substance-related problems. French and colleagues[33]

found that nurses who demonstrated caring behaviors toward the mothers whose infants were being treated for NAS were better able to help them recognize and interpret infant cues, thus enhancing mother-infant interactions. A basic competency of all NICU nurses is to promote mother-infant interactions; therefore, there can be no tolerance for judgmental attitudes toward mothers with substance abuse problems. All infants with NAS should be managed with nonpharmacologic nursing interventions as first-line treatment in an atmosphere of kindness and sensitivity. It has been long known that in a few cases for unknown reasons, that is all that might be needed to fully recover from NAS.[14,15,34]

## PHARMACOLOGIC INTERVENTIONS

The goal of pharmacologic intervention is to alleviate distressing and possibly painful withdrawal effects so that the infant may become comfortable enough to eat, sleep, and recover from physical dependence. It is well known that adults recovering from physical dependence can become very uncomfortable, reporting similar signs seen in infants such as perspiration, nausea, muscle spasms, abdominal cramping, and agitation. They also report signs that cannot be assessed in newborns, such as itching, chills, tension, severe anxiety, and depression.[35] Opioid withdrawal is best treated with opioids, given the opioid mechanisms of action.[36] The choice of pharmacologic interventions is often determined by previous experience, clinician preference, and information about the maternal drug use. There is little empirical evidence that guides pharmacologic management in this population, although well-designed studies are underway.

### Opioids

The most recent surveys available indicate that the majority of providers in the United States[37] and the United Kingdom[38] use an opioid (morphine or methadone) as the first drug of choice to treat confirmed opioid-induced NAS, as recommended by the American Academy of Pediatrics (AAP) in 1998[39] and again in 2012.[40] Since 1998, the recommendation is to use a drug from the same class as the cause of the withdrawal signs, and using morphine or methadone for opioid withdrawal.[40] Unfortunately, there are no large-scale, well-designed studies available to standardize the initial dose, escalation, or weaning of either morphine or methadone in infants, a limitation clearly defined by the AAP.[40] In 2010, Osborn and colleagues[34] updated their meta-analysis of all available randomized and quasi-randomized studies of opioids in the treatment of NAS. They concluded that, while there are not enough data to recommend that one opioid is better than another in treating NAS, given the severe limitations of the published studies, opioid treatment should be restricted to infants whose mothers used opioids.[34] Until the evidence provides a definitive regimen for treatment, clinicians should continue to evaluate the effects of the drugs, the doses, and dosing intervals, using a common withdrawal assessment instrument for which nurses have achieved a reasonable level of interrater reliability.

### Buprenorphine

Buprenorphine is a long-acting partial $\mu$ agonist (opioid) that has an established safety profile in pregnant women and other adults.[41,42] Because it has less respiratory depression than other agonists,[43] it is currently under investigation in infants with NAS. Two studies that evaluated the safety and dosing schedule have promising results. Results of the first study by Kraft and colleagues[44] prompted a higher starting dose, increased titration regimen, and higher maximum daily dose.[45] Although the authors reported a significant decrease in time of treatment and length of stay in the infants treated with buprenorphine, the study did not have enough power (estimated at 35%) for clinicians to have confidence in the statistical results. At best, a trend toward shorter length of stay and shorter treatment time was found in the 12 infants treated with buprenorphine. The authors combined the results of both of their studies ($n = 50$) and again reported statistically significant differences in length of stay but again without power to substantiate those results.[43] In addition, the authors excluded infants who were exposed to benzodiazepines during gestation. Despite these limitations, the authors established that buprenorphine is safe and efficacious in full-term infants with NAS who have been exposed only to opioids, which was their primary purpose. Additional studies are currently underway to expand the generalizability with more highly powered results. Dosing and weaning recommendations are still unavailable.

### Second-line drugs

Second-line drugs are medications often used in combination with opioids to manage specific clinical signs, but Osborn and colleagues[34,46] warn against using them as a first choice for opioid withdrawal. These drugs are indicated only when the baby has been prenatally exposed to benzodiazepines or develop signs that are not well controlled by the opioid class of drugs. Phenobarbital is preferred to diazepam in the reduction of central nervous system symptom severity and to avoid treatment failure.[46] In 1 study, phenobarbital worked better when a loading dose was given.[47] There is growing evidence to support the safety and

efficacy of clonidine in the NAS population,[48–51] and it has been reported that approximately 20% of NICUs in the United States use it.[52] A recent study of 68 infants compared length of treatment with morphine combined with clonidine against morphine combined with phenobarbital.[53] Those in the clonidine group ($n = 34$) had fewer treatment days but no difference in average total morphine dose. Infants in the phenobarbital group ($n = 34$) were treated an average of 3.8 months, although infants were discharged from the hospital significantly sooner.[53] More studies are underway on the outcomes of clonidine. There is no evidence, however, to support the use of chlorpromazine.[46]

### Feeding

In 2001, the AAP reversed its recommendation regarding breast-feeding for mothers on a methadone program.[54] Prior to 2001, the AAP recommendation virtually prohibited women from breast-feeding because their methadone regimen exceeded an arbitrary daily dose threshold. Methadone levels are very low in breast milk and in infants who are breast-fed.[55] Although there is evidence that women on methadone can safely breast-feed their infants, no new trials have been published on the topic since 2012. In 2006, Abdel-Latif and colleagues[56] reported in their study of 190 infants that breast-feeding decreased the length of treatment of NAS. Those results were replicated in a retrospective study of 28 infants,[57] where the NAS scores in breast-fed infants were significantly lower than the scores with formula and combination feedings. McQueen and colleagues[57] also reported a significant decrease in severity of NAS clinical signs in the breast-fed group ($P = .001$). Isemann et al[58] performed a retrospective chart review of 128 infants who were treated for NAS to identify factors associated with favorable outcomes. They reported that ingestion of mother's breast milk was significantly correlated to a shorter length of stay and shorter duration of treatment ($P = .02$). One disadvantage to breast-feeding was reported by Dryden and colleagues,[59] who found that 354 breast-fed infants exposed to prenatal methadone had a significantly greater postnatal weight loss than formula fed infants. They postulated that the increased weight loss might be the result of NAS effects, such as poor feeding, diarrhea, poor sleeping patterns, tachypnea and jitteriness, and an overall increased caloric expenditure, although another explanation might be inadequate dosing to control these clinical signs.

It has previously been established that breast-feeding may be protective against the development of severe NAS.[9] Dryden and colleagues[9] reported that 437 infants who breast-fed for at least 72 hours significantly reduced the odds of receiving treatment of NAS (odds ratio, 0.55; 95% confidence interval, 0.34–0.88; $P = .013$). Despite this evidence, several authors have reported that breast-feeding rates among women on methadone and with substance abuse problems are low, ranging around 24% to 27%.[59,60] Even among those mothers who initially chose breast-feeding, only 11% to 15% were still breast-feeding at the time of discharge.[59,60]

Unfortunately, not all women who deliver infants with NAS are in a treatment program. In many situations, substance abuse treatment that is gender specific and comprehensive is not available for this population.[61] In the situation in which a mother is not in treatment, the AAP does not recommend breast-feeding, because the infant can be exposed to many teratogens because of unpredictable doses. The AAP identifies illicit substances that are contraindicated because of known adverse effects, including amphetamines, cocaine, heroin, marijuana, and phencyclidine. The pharmacokinetics of many illicit substances in breast milk is unknown and difficult to study. Other contraindications include being positive for HIV when the mother is not on antiretroviral drugs.[62]

## CONCLUSIONS

Most of the evidence that guides management of infants with NAS is considered expert opinion. Experienced NICU nurses have exemplary assessment skills that enable them to anticipate the needs of infants with NAS and provide comfort measures that support them through the difficult transition of withdrawal. For decades, nursing care of infants with NAS has been guided by attending to the infants' clinical signs of withdrawal and stress. Many interventions have become the standard of care after having been in use since the 1970s.

Nurses choose interventions that support individual signs of stress. The standard of care should always be provided, such as decreasing environmental stimuli, holding the infant, providing nonnutritive sucking, swaddling, containment to gently restrain flailing limbs or head, and rubbing rather than patting. Other interventions need to be empirically tested in this population, such as vertical rocking and demand feeding. Data on the use of nonpharmacologic interventions such as aroma and music therapy, kangaroo care, massage, and use of nonoscillating water beds would also be very welcome in this population and provide the evidence needed to guide best practice. Even holding the infant might be investigated, because some NICUs use volunteers to hold infants with NAS when the mothers are unable to be in the NICU. Infants experiencing NAS often need constant surveillance to keep their clinical signs under control, a difficult task for a NICU nurse who is caring for 2 to 3 other infants. Could infant holding

decrease length of stay or impact the severity of NAS signs? Does the nurse-to-patient ratio effect these patient outcomes? Does a dedicated "NICU NAS Team" impact patient outcomes by decreasing length of stay?

Breast-feeding is recommended for women in a drug treatment program but only when they do not have specific contraindications such as untreated HIV. There is some evidence that infants with NAS who are breast-fed have decreased severity of clinical signs of withdrawal. Although further evidence is needed to establish its potential strength, there are no contraindications to providing skin-to-skin contact, especially when breast-feeding is contraindicated. There is also no evidence regarding the efficacy of demand or semidemand feedings in this population, another area of opportunity for nursing research.

Pharmacologic intervention is currently guided by AAP recommendations, which indicate that narcotic drug withdrawal should be treated with opioids. Morphine and methadone are most often used. The studies of buprenorphine have established only its safety profile in a small group of infants. More data are needed to test dosing regimens and compare outcomes with other opioids, so it should be used only in clinical trials until such evidence is available.

Most importantly, NICU nurses are encouraged to increase their knowledge base about the evidence that supports pharmacologic management of pregnant women who use illicit substances. They must also adopt a nonjudgmental attitude when caring for these infants and their mothers, so they may positively impact the maternal-child interaction. Mothers rely on feedback from NICU nurses who they perceive as experts about how they should interpret their infants' cues and how they should appropriately respond. They need to be taught not only interventions that decrease infant's signs of stress and withdrawal but also not to expect eye contact until the infant is ready. They must be reassured that eye contact avoidance is not because the infant does not love them; it is just too much stimulation at that time. Every nurse has the opportunity to impact someone's life with education and words of encouragement or praise, and that is a powerful and important role in the NICU.

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