

Neonatal Opioid Withdrawal Syndrome

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KEYWORDS

- Neonatal abstinence syndrome • Neonatal opioid withdrawal
- Perinatal substance abuse • Buprenorphine • Methadone

KEY POINTS

- It is important for all providers to recognize neonatal opioid withdrawal with shifts in maternal prescription opioid use and abuse.
- Current evidence points to a milder withdrawal syndrome with maternal buprenorphine maintenance in comparison with methadone.
- Initial treatment of neonatal opioid withdrawal should be with opioid monotherapy; currently there is no evidence to recommend one regimen over another. Adjunctive therapy, if required, should be with phenobarbital or clonidine.
- The hospital environment should be maximized to promote low stimuli for infants affected by withdrawal, and should include rooming-in and breastfeeding promotion where appropriate.
- At present there is limited evidence on the long-term childhood effects of perinatal opioid exposure, and support is needed for families during early childhood development.

BACKGROUND AND EPIDEMIOLOGY

Neonates who have had in utero exposures from maternal substance abuse can experience central nervous system effects of the drugs, including drug toxicity and withdrawal. Neonatal abstinence syndrome (NAS), initially described in the 1970s, is the term used for the constellation of withdrawal symptoms. The clinical features and treatment of withdrawal from opioids is a specific form of NAS, and has recently been termed neonatal opioid withdrawal syndrome (NOWS). This review focuses primarily on the presentation, diagnosis, and management of NOWS, with emphasis on current evidence for assessment by scoring systems, pharmacologic treatment protocols, and implications for future policy and research.

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The rising incidence of maternal opioid use is demonstrated by hospital discharge records revealing a nationwide increase from 1.19 to 5.63 per 1000 births per year from 2000 to 2009.¹ In 2012, an estimated 5.9% of women aged 15 to 44 years were using illicit drugs during pregnancy.² Marijuana use is most common, followed by use of prescription opioids and, less commonly, stimulants, heroin, and psychotropic drugs.³ Unique to the past several years is the rapid increase in prescription opioid abuse,^{1,4} which has changed both the number and demographic characteristics of pregnant women using illicit substances, necessitating providers of all geographic and socioeconomic populations to be aware of the management of neonatal opioid withdrawal.

The epidemic abuse of prescription opioids and continued heroin use have increased the rates of NAS from 1.20 per 1000 births in 2000 to 3.39 per 1000 births in 2009, with an estimated 1 newborn per hour born with NAS in the United States in 2009.¹ Health care spending for illicit drug use during pregnancy and related neonatal outcomes has increased from an average of US\$39,400 per NAS hospital admission in 2000 to \$53,400 in 2009, with 77.6% of these charges attributed to state Medicaid in 2009.¹ The length of stay for NAS averages 16 days and has not significantly changed during this time.¹ According to a recent survey, only about half of neonatal intensive care units (NICUs) in the United States have a written protocol for the diagnosis and management of NAS, which represents an important area for educational improvement.⁵

CLINICAL PRESENTATION AND DIAGNOSIS

Mothers who are abusing opioids may be identified during prenatal care and referred to perinatal substance abuse programs, which will optimally have an affiliated neonatal program. Unfortunately many women with opioid addiction do not obtain prenatal care, and are first seen when they present in labor. Some women, particularly those with addiction to prescription opioids, may be able to obtain a prescription from other physicians or purchase diverted “street drugs” during the pregnancy, and the neonatal exposure will be unsuspected until the withdrawal syndrome develops. Risk factors for maternal drug abuse include poor or no prenatal care, a previously unexplained late fetal demise placental abruption, unexplained intrauterine growth restriction, maternal hypertension, and precipitous labor.^{6,7} These factors, clinical suspicion of opioid withdrawal, or a known history of maternal drug abuse or opioid replacement therapy may prompt screening with a maternal or neonatal urine drug screen or meconium toxicology testing. The legal implications of this screening are important to consider before initiation, as several states consider a positive newborn urine drug screen to be evidence of child abuse.⁸ The optimal urine sample for neonatal screening is the first urine after birth, as many substances are quickly metabolized and become undetectable.⁷ Urine testing can result in false positives, as some prescription medications and over-the-counter products cross-react with testing for drugs of abuse, so that a positive test on the screening procedure requires confirmatory testing by gas chromatography or mass spectrometry.⁸ Drugs that are metabolized by the fetal liver and kidneys are concentrated in meconium, which can detect prenatal substance exposure that has occurred months before birth; therefore, meconium testing may be positive when urine testing is negative.^{7,8} Analysis of neonatal hair or umbilical cord tissue can also provide a window of screening of weeks to months, but are primarily used only for research purposes at present.⁸

The probability of newborns exposed to maternal chronic opioid use developing withdrawal symptoms that are sufficient to require pharmacologic therapy varies

widely in studies, and likely depends on the composite of substances prescribed to or abused by the mother as well as genetic, epigenetic, and environmental factors.⁹ The effects of illicit drugs on fetal development are related primarily to abnormal growth and alterations in neurotransmitters and brain development, rather than major structural teratogenic effects.¹⁰ Beyond the drugs themselves, behaviors of women who chronically abuse substances may also lead to neonatal problems resulting from poor access to or compliance with prenatal care, poor nutrition resulting in reduced delivery of nutrients to the fetus, increased rates of mental illness and interpersonal violence, and exposure to infections including human immunodeficiency virus (HIV) and hepatitis C.^{9,11}

Opioid exposure in utero leads to a well-described complex of withdrawal signs and symptoms that can be described as NOWS. Studies have shown that 21% to 94% of neonates exposed to opioids in utero will develop withdrawal signs and symptoms that are severe enough to warrant pharmacologic treatment.^{7,12,13} Factors that affect the likelihood and severity of NOWS include the specific opioid exposure, dose of opioid replacement therapy, gestational age, polysubstance abuse, tobacco, and breastfeeding.

Methadone, a full opioid μ -receptor agonist, has been the standard of care for opioid treatment in pregnancy in the United States since the 1970s.¹⁴ The use of buprenorphine, a partial μ -receptor antagonist, for opioid addiction in pregnancy appears to have increased rapidly since the 2010 MOTHER trial, and other recent studies, demonstrated less severe neonatal opioid withdrawal and equivalent obstetric outcomes.^{9,15–17} Several studies have demonstrated that the dose of methadone replacement therapy is not related to the incidence or severity of withdrawal, and methadone should be titrated to alleviate maternal withdrawal symptoms and cravings for illicit drug use.^{18–21} However, other studies have shown a higher likelihood of infants requiring pharmacologic treatment for withdrawal with higher doses of methadone, especially when increased or initiated near term, or when combined with benzodiazepine abuse.^{22–26} Women who have been on long-term methadone maintenance therapy before conception appear to have more favorable outcomes.²⁷ Most experts agree that maternal methadone treatment should not be decreased to prevent neonatal withdrawal severity, as the higher likelihood of a relapse of opioid abuse increases the incidence of poor pregnancy outcomes, including intrauterine growth restriction and preterm delivery.^{28,29} Compared with methadone-exposed infants, buprenorphine-exposed infants in the MOTHER trial required less morphine, had shorter hospital stays, and had a shorter duration of treatment for neonatal withdrawal syndrome, with no significant differences in adverse maternal or neonatal outcomes.¹⁷ There is also no evidence for a dose-response relationship between maternal buprenorphine dose at the time of delivery and neonatal outcomes, including severity of withdrawal or need for pharmacologic treatment.³⁰ In one study, male infants exposed to buprenorphine had higher mean withdrawal scores and required pharmacologic therapy more often than their female counterparts, possibly pointing to a gender-specific association.³¹ This same relationship has been disproved with methadone-exposed infants.³² Differences in neonatal withdrawal with methadone and buprenorphine are described in **Box 1**.

Symptoms of NOWS commonly begin within 24 to 72 hours after birth, the average time of onset being dependent on the half-life of the substance. The American Academy of Pediatrics recommends observation of opioid-exposed neonates in the hospital for 3 days for short-acting opioids and up to 5 to 7 days for long-acting opioids,⁷ as the need for initiation of pharmacologic treatment can occur up to 120 hours of life.^{6,7,9} Infants exposed to minimal episodic use of opioids for medical indications such as

Box 1	
Methadone versus buprenorphine in neonatal withdrawal	
Methadone	Buprenorphine
Full μ -receptor agonist	Partial μ -receptor antagonist
Likely no dose-response relationship ¹⁸	No dose-response relationship ³⁰
Likely no gender-specific relationship ³²	
Possible faster time to withdrawal ³⁴	Possible slower time to withdrawal ³⁴
Increased severity with benzodiazepenes ³⁹	Lower peak Finnegan scores ¹⁷
	Shorter hospital stays ¹⁷
	Shorter duration of treatment ¹⁷

migraine headache or musculoskeletal pain appear to be at minimal risk for neonatal withdrawal requiring pharmacologic treatment; however, it is often difficult to assess the degree of exposure. When the degree of exposure is uncertain, the authors recommend observing infants in the hospital for at least 96 hours. Studies of methadone concentration in cord blood have noted that lower starting concentrations of methadone and more rapid decline in levels are associated with more severe symptoms of withdrawal.³³ In one study, infants exposed to methadone in utero had a shorter time to withdrawal than infants exposed to buprenorphine, independent of other demographic factors (34 vs 71 hours).³⁴ The pathophysiology of neonatal opioid withdrawal can be explained by the presence of opioid receptors in the brain and gastrointestinal tract, leading to mostly central nervous system, autonomic system, and gastrointestinal signs and symptoms.⁷ Signs and symptoms are summarized in

Box 2.

Several features of opioid withdrawal in neonates are nonspecific and may be associated with other serious conditions. The knowledge of maternal substance abuse during pregnancy should not preclude careful consideration of a differential diagnosis, including infection, hypoglycemia, hypocalcemia, hyperthyroidism, intracranial hemorrhage, hypoxic-ischemic encephalopathy, or maternal use of selective serotonin reuptake inhibitors (SSRIs).⁷

Several special populations may present differently from the classic syndrome described. Preterm infants may have less severe or less prolonged presentations because of neurologic immaturity, less cumulative drug exposure, or less drug retained in fat stores.^{7,26} Infants affected by maternal polysubstance abuse may have differing presentations from those exposed to opioids alone.³⁵ Benzodiazepines, though not well studied, can cause a withdrawal picture similar to opioid withdrawal including hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, and tachypnea.^{7,36} Withdrawal from benzodiazepines can therefore cloud the clinical picture and potentially lead to prolonged treatment of opioid withdrawal.^{35,36} SSRIs also have a similar withdrawal picture in neonates, including irritability, poor suck, feeding difficulties, tremors, hypertonia, tachypnea, and sleep disturbances, although symptoms are usually not severe enough to require medication.^{7,37,38} In a 2008 study from Boston, benzodiazepine use combined with methadone use significantly increased the length of stay in hospital by 5.88 days in comparison with methadone alone.³⁹ This finding was similar to those of prior studies of concurrent methadone and benzodiazepine use, which also showed an increased length of neonatal hospitalization for withdrawal.^{24,25} In these same studies, neither maternal SSRI use nor tobacco use while on methadone increased adverse outcomes.^{25,39} However, other studies have shown higher peak NAS scores among infants born to women smoking 20 or more cigarettes a day when compared with lighter or never smokers.⁴⁰

Box 2**Clinical features of neonatal opioid withdrawal**

Central Nervous System

- High-pitched cry
- Irritability
- Exaggerated primitive reflexes
- Hyperactive deep tendon reflexes
- Increased tone
- Altered sleep-wake cycles
- Tremors
- Seizures

Gastrointestinal

- Vomiting
- Loose stools
- Poor feeding
- Uncoordinated, constant sucking
- Failure to thrive

Autonomic Dysfunction

- Sweating
- Sneezing
- Temperature instability
- Nasal stuffiness
- Yawning

Adapted from Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics* 2012;129:e540–60.

PATHOPHYSIOLOGY OF NEONATAL OPIOID WITHDRAWAL

The pathophysiology of neonatal opioid withdrawal includes the contributions of fetal genetics, fetal response to maternal withdrawal symptoms stemming from reduced levels of opioids passed to fetal circulation, effects of stress responses in the fetus in reaction to maternal physical condition, and evidence of abnormalities in brain electrical activity as observed by continuous electroencephalographic (EEG) monitoring. The fetal propensity for neonatal opioid withdrawal may be influenced by the genes responsible for 2 proteins associated with opioid addiction in adults. The single-nucleotide polymorphisms affecting the μ -opioid receptor (*OPRM1*) and catechol-O methyltransferase (*COMT*) genes have an association with greater risk of adult addiction to opioids.⁴¹ These polymorphisms have protective effects for infants treated for neonatal opioid withdrawal, including shortened length of hospital stay, less need for any pharmacologic treatment, and less need for treatment with 2 or more medications.⁴¹

The likelihood of an infant developing opioid withdrawal may be associated with the timing and quantity of opioids transferred to the developing fetal brain. The duration of

use of a specific dose of any opioid that is sufficient to result in neonatal withdrawal is unknown and, as previously described, the literature has contradictory findings regarding the effects of methadone dose on neonatal risk of withdrawal.^{18,23,24} The variability of purity of street heroin in communities over time combined with the intermittent availability of opioids being procured for substance abuse may result in intra-uterine fetal withdrawal. Neither disclosure of extent and duration of opioid use, nor current methods of detection of opioids in biological fluids, can accurately estimate the extent of exposure to the fetus.

The clinical features of neonatal opioid withdrawal include observed seizures, which are often more heavily weighted in the scoring system, suggesting a relationship to more severe withdrawal. Clinical observation may not detect subtler abnormalities of electrical transmission in the brain as evidenced by continuous amplitude-integrated EEG tracings, as one study found that 6 of 8 infants exposed to opioids had subclinical seizures that did not require treatment in the first 3 days of life.⁴²

Sleep disorganization contributes to the severity of opioid withdrawal, as shown by continuous EEG monitoring of patients receiving treatment for NAS compared with nonopioid-exposed controls.⁴³ The observations of disordered sleep accompanied by subclinical seizures suggest alterations of brain electrical activity, which may correlate with clinical observations of a delay in opioid-exposed infants developing normal sleep-wake cycles in the first months of life.

Conceptualization of the pathophysiology of neonatal opioid withdrawal may in the future include genetic analysis to guide interventions; however, clinicians will continue to apply clinical expertise to guide such interventions. The brain disturbances revealed by continuous EEG monitoring may provide greater fine-tuning for intervention during hospitalization. The maturation of brain systems and the effects on the clinical scoring as infants mature may result in a need to adjust clinical evaluation and NAS scoring for those infants hospitalized for longer stays. An improved understanding of sleep alterations may affect clinical management and anticipatory guidance at discharge from the neonatal units.

SCORING METHODS

Depending on the drug exposure experienced by each infant, the time frame for withdrawal can vary. Most experts agree that monitoring for at least 72 to 120 hours after birth is sufficient to recognize the symptoms of withdrawal, although with long-acting opioids in particular, such as methadone, the withdrawal period can be longer.⁷

Several scoring tools are available for measuring signs and symptoms of withdrawal and to determine when to start therapy, based primarily on observations from opioid withdrawal.⁴⁴ The most commonly used scale in the United States is the modified Finnegan Neonatal Abstinence Scoring system (**Fig. 1**).^{7,45} This comprehensive tool is completed every 4 to 6 hours with items covering central nervous system, autonomic, vasomotor, and gastrointestinal signs and symptoms. In a study of normal newborns, the average Finnegan score at days 1 to 3 of life was 2, but variation occurred up to a 95th percentile of 7, therefore scores of 8 or higher were considered pathologic.⁴⁶ This knowledge that all newborns display some level of Finnegan scoring immediately after birth in comparison with 5 to 6 weeks of life is important when caring for infants with prolonged hospitalizations.⁴⁶ A typical protocol is to reevaluate an infant scoring more than 8 within 1 hour, with initiation of medication if the score is consistently high. Other scoring tools are also available, including the Lipsitz Neonatal Drug-Withdrawal Scoring System, the Ostrea tool, the Neonatal Withdrawal Inventory, and the Neonatal Narcotic Withdrawal Index.⁶

NAME: _____

MR#: _____

Nursing Instructions
 1. If infant scores >8, rescore in one hour
 2. Notify physician if two scores, 1 hour apart, >8
 3. Give medication as prescribed by physician every 3-4 hours. Do not exceed 4 hours in dosing.

Initiation of morphine sulfate therapy:
 CATEGORIES SCORE Morphine= Morphine Sulfate oral solution
 0 0-8 0 0.4 mg/ml
 I 9-12 0.04 mg
 II 13-16 0.08 mg
 III 17-20 0.12 mg
 IV 21-24 0.16 mg
 V >=25 0.20 mg

SIGNS AND SYMPTOMS	SCORE	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
		/time	/time	/time	/time	/time	/time	/time	/time	/time	/time	/time	/time	/time
Excessive Cry	2 - 3													
Sleeps < 1 hour after feeding	3													
Sleeps < 2 hours after feeding	2													
Sleeps < 3 hours after feeding	1													
Hyperactive Moro Reflex	1													
Markedly Hyperactive Moro Reflex	2													
Mild Tremors: Disturbed	1													
Moderate-Severe Tremors: Disturbed	2													
Mild Tremors: Undisturbed	1													
Moderate-Severe Tremors: Undisturbed	2													
Increased Muscle Tone	1-2													
Excoriation (specific area)	1 - 2													
Generalized Seizure	8													
Fever > 37.2 C	1													
Frequent Yawning	1													
Sweating	1													
Nasal Stuffiness	1													
Sneezing	1													
Tachypnea (Respiratory Rate> 60/min)	2													
Poor Feeding	2													
Vomiting	2													
Loose Stools	2													
Failure to Thrive (weight gain ≥ 10% below birth weight)	2													
Excessive Irritability	1 - 3													
TOTAL SCORE / CATEGORY														
INITIALS														

Fig. 1. Modified Finnegan scoring system. (From Jansson LM, Velez M, Harrow C. The opioid exposed newborn: assessment and pharmacologic management. J Opioid Manag 2009;5:47-55. Adapted from Finnegan L, Connaughton J, Kron R, et al. Neonatal abstinence syndrome: Assessment and management. Addict Dis 1975;2:141-58.)

There are no studies comparing the efficacy or future impact of evaluation and pharmacologic treatment based on the use of each of the scoring methods.⁴⁴ There are also no studies comparing outcomes with initiation of therapy at different scoring thresholds. It is important for each institution to establish a standardized system for routine monitoring, scoring, and initiation of therapy that fits the needs of their individual patient population. The subjective nature of the evaluation of some of the signs and symptoms of withdrawal can lead to poor reliability, especially when the examiners are not frequently involved in the care of infants with withdrawal symptoms.

PHARMACOLOGIC TREATMENT

The primary goals of treatment during neonatal withdrawal are to alleviate short-term symptomatology to allow healthy feeding, growth, and maternal bonding. There are severe potential consequences of not initiating treatment, including seizures, severe weight loss, failure to thrive, and possibly death, but ultimately withdrawal is thought to be a self-limited process.¹⁰ At present there are no studies delineating the long-term benefits of treatment. There is also significant heterogeneity in treatment patterns in

the United States and internationally, and a need for further research to delineate optimal pharmacologic treatment of neonatal withdrawal.²⁹ When initiating any opioid therapy, it is important to monitor for oversedation in the infant by careful nursing observation, including monitoring for apnea, and assessment of respiratory rate and oxygen saturation.⁴⁷

Opioid monotherapy is currently the most common pharmacologic treatment for neonatal opioid withdrawal.^{6,44} A 2010 Cochrane review found that opioid therapy was superior to supportive care in respect of time to regain birth weight, but resulted in prolonged stay in hospital.⁴⁸ This review also found that opioids significantly reduced treatment failure in comparison with diazepam but not in comparison with phenobarbital. In addition, there were insufficient data to recommend treatment with any one opioid over another.⁴⁸ A confounding factor in many of these studies was polysubstance abuse, resulting in a post hoc analysis hypothesis by the Cochrane group that infants exposed primarily to opioids may fare better with opioid-only treatment. Despite the cited methodological flaws with many of the studies used for this Cochrane article, opioids are recommended as the first-line therapy in this review as well as by most professional organizations.^{7,48}

Historically, NAS was treated with tincture of opium combined with alcohol, or paregoric, a combination of multiple ingredients, several of which are now known to be toxic to infants.⁶ Opioids used currently include formulations of morphine, methadone, and, most recently, buprenorphine.²⁹ Morphine preparations currently in use are short-acting ethanol-free preparations administered every 3 to 4 hours based on their short half-life, although the pharmacokinetics of oral morphine in newborns is unknown and there can be significant interpatient variability.²⁹ There is currently no evidence or agreement on the optimal oral morphine regimen, or a safe maximum daily dose, although published studies report an average of 0.06 to 0.24 mg/kg/d.²⁹ The protocol used in the MOTHER trial was not weight based, and instead escalates the dose based on the Finnegan score. The authors have successfully adapted this protocol for use in infants at the University of New Mexico (**Box 3**). Each institution should aim to create or adopt a standardized protocol until more information becomes available.

Methadone's longer half-life presents benefits and challenges when used for neonatal opioid withdrawal. Longer intervals between doses may facilitate outpatient therapy; however, this is accompanied by a longer duration of therapy when used for buprenorphine-exposed neonates,¹⁷ and newborn pharmacokinetics are largely unexplored.²⁹ According to a 2006 survey, only about 20% of NICUs in the United States were using methadone.⁵ There is only one study comparing morphine with methadone for in utero methadone or heroin exposure, with no significant difference in length of stay in hospital.⁴⁹ Further studies are needed to determine ideal treatment populations, regimens, and comparisons with other opioid therapies. A sample treatment protocol for methadone therapy in neonatal withdrawal is presented in **Box 4**.

As a novel therapy for neonatal opioid withdrawal, buprenorphine has only limited data. Two recent studies at the same institution have shown that buprenorphine is a safe alternative for treatment of neonatal opioid withdrawal, and resulted in a shorter length of stay when compared with morphine. However, more infants required adjunctive therapy with phenobarbital.^{50,51} Further studies are needed before buprenorphine can be used for the treatment of neonatal withdrawal outside of a research setting.

In addition to opioid therapy, several other medications are in use as adjunctive therapy, primarily for infants with persistent severe symptoms after monotherapy with an opioid. Some experts also believe that cotherapy combining an opioid with

Box 3**University of New Mexico protocol for short-acting morphine for neonatal opioid withdrawal**

Dose given every 3–4 h with feeds; do not exceed 4 h between doses of morphine (0.04 mg/0.1 mL)

A. Score Dose for Initiation (based on modified Finnegan score)

- 0–8 None
- 9–12 0.04 mg/dose
- 13–16 0.08 mg/dose
- 17–20 0.12 mg/dose
- 21–24 0.16 mg/dose
- 25 or above 0.20 mg/dose

B. Score Morphine Initiation

- If neonate scores 9–12, rescore after feeding or within the hour and if rescore is 9–12, start treatment based on highest score. If rescore is 0–8, do not initiate treatment
- If initial score is 13 or greater, start treatment immediately without reassessment

C. Morphine Maintenance/Escalation

- Maintain dose if score 0–8
- Increase dose by 0.02 if score is 9–12 (rescore before dosing)
- Increase dose by 0.04 if score 13–16
- Increase score by 0.06 if score 17–20

D. Weaning Instructions

- Maintain on dose 48 h before starting weaning
- Wean 0.02 mg morphine every day for a score of 0–8
- Defer wean for score 9–12

E. Re-escalation

- If neonate scores 9–12, rescore as described for initiation
- If second score is 9–12, increase morphine 0.01 mg every 3–4 h
- If 2 consecutive scores 13–16, increase 0.02 mg every 3–4 h
- If 2 consecutive scores 17–20, increase 0.04 mg every 3–4 h, etc

Timing of scoring: Hospitalized infants are scored every 3–4 h before feeds. Reassessment occurs immediately after feeds or within 1 hour.

Oxygen saturation and respiratory rate is assessed 30–60 minutes after first 2 doses and after any dose escalation.

Adapted from Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363:2320–31.

phenobarbital as the initial treatment may be beneficial for infants with polysubstance exposure, but there is currently no consensus of evidence to support this.²⁹ The only trial examining the effects of initial combination therapy with opioids and phenobarbital demonstrated benefits of shorter hospital stay, less severe withdrawal, and less hospital cost.⁵² A recent randomized controlled trial using clonidine as adjunctive therapy demonstrated a shorter length of treatment and less opioid requirement for infants cotreated with clonidine.⁵³ Adverse outcomes were also seen in this study,

Box 4**University of New Mexico methadone protocol for neonatal opioid withdrawal syndrome**

Step 1: 0.7 mg/kg/24 h divided into 6 doses (every 4 h) is starting dose

Step 2: Decrease dose by half, which is 50% of starting dose every 4 h

Step 3: Same dose, which is 50% of starting dose every 6 h

Step 4: Same dose, which is 50% of starting dose every 8 h

Step 5: Same dose, which is 50% of starting dose every 12 h

Step 6: Decrease dose by half, which is 25% of starting dose every 12 h

Step 7: Same dose, which is 25% of starting dose every 24 h

Use with nurses' expertise when decreasing doses. Decrease doses based on daily assessment of needs. Each baby is different and will score individually.

If scores are >8 three consecutive times or if the mean score of three consecutive scores is >8 or if the scores are >12 two consecutive times, then continuing present dose and interval may be necessary. Observe for 48 h after last dose. If infant has gained weight rapidly, it may be necessary to adjust dose by using current weight as the basis for calculating the current dose while maintaining the current interval.

Any infant with severe NAS in Level 1 newborn nursery requiring escalation of methadone dose to greater than 0.7 mg/kg/24 h or the addition of clonidine as an adjunctive pharmacologic treatment should be transferred to Level 2 nursery for evaluation and monitoring.

including greater rebound withdrawal and need for reinitiation of opioid therapy in the clonidine group, as well as possibly unrelated outcomes of myocarditis and sudden infant death syndrome indicating the need for more observation.⁵³ In addition, a recent prospective study of adjunctive therapy with an opioid plus clonidine versus phenobarbital found a shorter stay in hospital with phenobarbital, but an overall longer treatment time when compared with clonidine.⁵⁴ Additional studies are needed to determine the safety and efficacy of using phenobarbital or clonidine in conjunction with an opioid to decrease withdrawal severity.^{55,56} A 2010 Cochrane review of studies on adjunctive therapies concluded that opioid monotherapy remains superior for the treatment of neonatal opioid withdrawal.⁵⁶

NONPHARMACOLOGIC TREATMENT

Box 5 summarizes several aspects of nonpharmacologic therapy that are beneficial for NOWS and should be initiated in any infant at risk.⁴⁴ Because infants experiencing withdrawal are hyperarousable and have altered sleep/wake states, ensuring a dark, quiet environment with low stimuli is essential in determining the true need for medications and avoidance of false elevation of scoring. Swaddling, skin-to-skin, pacifiers, and "cluster care" to minimize stimulation are also common practices thought to be beneficial.^{57,58}

Several studies have explored complementary and alternative medicine techniques for neonatal withdrawal. Massage therapy and physical therapy can be used to treat hypertonicity and overstimulation.⁵⁸ Music therapy has been shown to calm infants and regulate sleep patterns, and lavender aromatherapy and exposure to the mother's scent have been shown to reduce stress and decrease cortisol levels in infants.^{58,59} Acupuncture is commonly used for adult detoxification, and the use of acupuncture or acupressure in neonates offers another potential alternative treatment for neonatal withdrawal.⁶⁰

Box 5**Nonpharmacologic interventions**

Hyperarousability

- Cluster care
- Dark, quiet environment
- Swaddling
- Skin-to-skin
- Music therapy
- Aromatherapy

Hypertonicity

- Physical therapy
- Massage

Mother-Infant Bonding

- Breastfeeding support
- Rooming-in where possible
- Family education
- Maternal opioid maintenance programs

The initial appropriate hospital setting for newborns can vary between institutions and by clinical severity.⁴⁷ Possible options for infants at risk for opioid withdrawal include the NICU, an intermediate-care Level 2 nursery, a Level 1 nursery apart from the mother, or rooming-in of baby with the mother in a regular postpartum unit. The practice of rooming-in has been shown in recent studies of neonatal withdrawal to decrease NICU admission, need for treatment, and length of stay, and to increase the likelihood of discharge in the mother's custody.^{61,62} Fostering the mother-infant dyad early in the neonatal period through examinations in the mother's room, and teaching mothers to respond to infant behavior, can improve nurturing behaviors crucial to infant development.⁶³ At the University of New Mexico, infants are routinely admitted to dyad care on the Mother-Baby unit; however, infants requiring escalation of the methadone dosing beyond the initial 0.7 mg/kg/24 hours, the addition of clonidine as adjunctive therapy, or gavage feedings to maintain adequate intake are transferred to the Level 2 nursery or NICU.

The role of breastfeeding in the management of neonatal opioid withdrawal has been the focus of several recent studies. As rooming-in helps support breastfeeding, it can be difficult to elucidate which practice is responsible for the improved outcomes. Buprenorphine and methadone enter breast milk in small amounts, and are considered to be safe regardless of the maternal dose of opioid replacement therapy.^{57,64} As buprenorphine is not well absorbed orally, infant exposure through breast milk may be limited to absorption from the oral mucosa. Several studies have demonstrated significant benefits of breastfeeding in neonatal withdrawal, including less requirement for pharmacologic treatment, shorter duration of treatment, and shorter hospital stays, regardless of type of drug exposure or gestational age.^{13,22,26,65,66} Most professional organizations including the American College of Obstetricians and Gynecologists,⁶⁷ the American Academy of Pediatrics,⁶⁸ and the Academy of Breastfeeding Medicine⁶⁹ now endorse breastfeeding in neonatal withdrawal if

women have been stable on opioid replacement therapy before delivery and there are no other contraindications such as active substance abuse, hepatitis C with nipple trauma, or HIV. It is important to counsel women in the prenatal period and to encourage breastfeeding where appropriate, as many women will encounter guilt regarding their history of substance abuse and may be discouraged by outside parties who are not aware of the benefits of breastfeeding for neonatal withdrawal. In a study in Maine of 85 mother-baby pairs in a long-term buprenorphine program, 76% of women chose to breastfeed, and 66% of these women continued up to 6 to 8 weeks after birth.⁶⁵ In addition, breastfed infants had lower peak Finnegan scores and less requirement for pharmacologic therapy than bottle-fed infants in the same group.⁶⁵ In a large study in Boston of 276 mother-baby pairs on methadone or buprenorphine, only 24% of eligible mothers attempted breastfeeding at the hospital, and 60% of these women stopped within 1 week.⁷⁰ It is therefore important for providers to understand the eligibility and benefits of breastfeeding for neonatal opioid withdrawal, and support mothers who do not have contraindications throughout the initial hospital postpartum period and beyond.

DEVELOPMENTAL AND FAMILY OUTCOMES

There is limited information about the long-term effects of maternal opioid exposure and neonatal opioid withdrawal or treatment on infant development. Confounding factors include exposure to multiple substances, coexisting psychiatric and medical problems in mothers, and the ongoing socioeconomic sequelae of drug abuse. Opioid exposure may alter the development of synaptic connections and lead to problems with maturation of signaling circuitry.⁷¹ Prenatal opioid exposure may also cause neurochemical and neurobehavioral adaptation in the fetal brain to achieve neurotransmitter signaling homeostasis, and result in interruption of normal brain function with long-term deficits.⁷¹ Efforts to regulate in the μ -opioid receptor systems, the serotonin system, and the dopamine system become evident after delivery with loss of exogenous opioid. Withdrawal symptoms represent the earliest abnormalities in the infant responding to an environment without exogenous opioids until replacement treatment begins if needed. The combined effects of reregulation after birth or treatment with morphine or methadone may contribute to further developmental concerns. Recent studies comparing well-matched controls with methadone-exposed infants have shown subtle differences in neurocognitive functioning and motor development early in infancy that persist at several months of life.^{13,72}

Efforts to characterize effects of prenatal drug exposure on specific brain regions have focused on imaging methods such as volumetric magnetic resonance imaging (MRI), functional MRI and magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI), which provide information about functional, metabolic, and region-specific variations in the brain, respectively. Using these methods, infants with prenatal cocaine and methamphetamine exposure had reduced brain volume in the dopamine neurotransmitter-rich putamen and subcortical areas, suggesting diffuse and long-lasting alterations in the brain.⁷³ However, functional MRI and MRS studies found possible compensatory processes from injuries caused by prenatal exposure, raising the possibility of developmental and neuroplastic brain recovery.⁷³ These MRI findings suggest a need for future research examining brain regions that may lead to improved knowledge regarding developmental outcomes for infants with prenatal opioid exposure.

Studies attempting long-term developmental follow-up present multiple challenges, and investigators agree that postnatal environmental factors have a primary

impact on early childhood outcomes. However, recent meta-analyses of long-term developmental outcomes came to the clear conclusion that when opioid-exposed infants were compared with opioid-free controls, there was consistent evidence of neurodevelopmental impairment, regardless of the age at testing or the tool used to assess these infants.⁷⁴ In an Australian cohort study, opioid-exposed infants had significantly lower scores with all assessment tools used, except for the psychomotor development index of the Bayley Scales of Infant Development. The differences appeared significant for cognitive function at the 18-month assessment persisting to the 3-year assessment measured with the Stanford Binet Intelligence Scale and the Reynell language scales.⁷⁴ Social maturity was also significantly lower for opioid-exposed children than for control children at 3 years.⁷⁴

In the context of findings suggesting short-term and long-term challenges to normal infant and early childhood development, it is clear that treatment of mothers in a structured program for opioid dependence is beneficial to the newborn, in comparison with no therapy.²⁹ Infant outcomes after prenatal opioid exposure may be improved by modifying the biopsychosocial conditions of their parents starting in the newborn period. This process can begin as described herein, with rooming-in and breastfeeding support in units designed to treat neonatal opioid withdrawal where parents may receive professional support in providing the daily health and nurturing activities needed by the infants. Unfortunately, after hospital discharge very little comprehensive long-term medical and mental health care is commonly provided to families for the complicated health issues associated with opioid abuse and neonatal development after opioid withdrawal.

Women with substance-abuse disorders commonly have coexisting mental health disorders, which may worsen in the postpartum period because of an altered hormonal milieu and sleep patterns. This situation may also be exacerbated when their newborns require inpatient care for neonatal withdrawal. Many of the women with dual diagnoses have difficulties with the structure and routines of the inpatient wards, and find themselves in conflict with the professional staff over behaviors such as taking a cigarette break or returning to the unit after leaving the hospital for the drug treatment center to access daily methadone. Experienced hospital staff should meet with the parent and develop a supportive plan for the time the mother can spend on the unit or rooming-in. Long-term prospects for maintaining custody of the child by the mother varies by hospital policies with respect to reporting to the child protection authorities, the clinical decision making around obtaining urine or other body substance drug screens, the availability of drug screens, and medical and forensic interpretation of the results.

AREAS FOR IMPROVEMENT

While there continue to be gaps in scientific knowledge, there are also many gaps in systems and biopsychosocial knowledge of neonatal withdrawal. Only about half of NICUs in the United States have a written protocol for the diagnosis and management of NAS.⁵ Nurses working in the NICU also report frustration and burnout from caring for infants with withdrawal, and may underestimate the skill and importance of caring for these newborns.⁷⁵ Support of families in the hospital environment while their child undergoes treatment for neonatal opioid withdrawal must address a broader set of needs, foremost among which is the ongoing medication-assisted treatment of the mother on methadone or buprenorphine. Lactation support systems are need to improve breastfeeding rates for opiate addicted women who are considered appropriate candidates to initiate breastfeeding. Many parents who have a history of

substance-use disorders also confront insecure housing, inadequate access to food, and lack of transportation. The hospital system and its staff need to understand the challenges parents may face in being present at their child's bedside for the amount of time the unit professionals deem important. Greater consideration of the social, historical, and political influences of society on the medical phenomenon of neonatal abstinence will help strengthen research and improve outcomes for mothers and babies.⁷⁶

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