5

Neonatal Abstinence Syndrome

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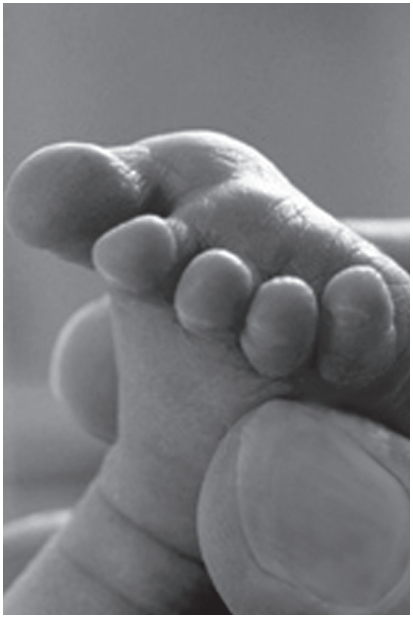

Introduction

Neonatal abstinence syndrome (NAS) is recognized as the effect of intrauterine exposure to substances that can cause physical dependence.[1] In other words, it is withdrawal of the neonate from substances that the mother ingested during pregnancy. Addiction is a behavior-related problem, which is different from physical dependence. It is important to distinguish between addiction and physical dependence. Babies are born physically dependent on substances (particularly opiates) and can become seriously ill due to abrupt discontinuation

of them. However, babies are NOT born addicted to drugs. Opiate withdrawal is the most common and most studied withdrawal syndrome. For purposes of this chapter, NAS will refer to opiate withdrawal.

The incidence of NAS following in utero exposure is reported between 55 and 94%.[2] From 2000 to 2009, a three-fold increase in the incidence was reported.[3] This correlates to the reported five-fold increase in opiate use during pregnancy over the last 10 years.[4] One study found that although infants born to substance-abusing mothers accounted for 2.9% of hospital births, they accounted for 18.2% of neonatal intensive care bed days demonstrating the economic burden this problem can create.[5] Furthermore, long hospital stays can disrupt family life and affect an infant's attachment to his or her parents.[6]

NAS is associated with chronic use at or near the time of delivery. If more than 2 weeks have passed since the last exposure, then withdrawal in the newborn is unlikely. Onset of withdrawal can range from 3 to 14 days and varies depending on several factors, including half-life of the substance and time of last exposure. The American Academy of Pediatrics (AAP) Policy Statement on NAS recommends that infants exposed to short-acting opiates (e.g., hydrocodone, oxycodone) be monitored for 3 to 5 days for signs and symptoms of NAS and those exposed to longer acting opiates (e.g., methadone) be monitored for 7 days prior to discharge from the hospital.[7] If a baby requires treatment, lengths of stay vary greatly. Most infants are treated in an inpatient setting until pharmacologic treatment is complete, but some are discharged to home to complete their treatment.

Substances of Abuse

There are multiple substances of abuse, and many users will abuse more than one substance leading to multiple exposures in the infant. Marijuana may be one of the most frequently abused substances, but its use is not associated with withdrawal in infants. Because cocaine causes a psychological addiction but does not result in a physical dependence, it is not associated with withdrawal in infants. When cocaine is used in conjunction with opiates, symptoms associated with the opiate withdrawal may be worsened. Maternal opiate and benzodiazepine use are both associated with withdrawal in the neonate.

Serotonin reuptake inhibitors (SSRIs) are not associated with NAS. The irritability that results from maternal SSRI use is referred to by some as *serotonin discontinuation syndrome*.[7] This self-limiting condition occurs early

after birth with symptoms mimicking NAS and usually resolves in 48 to 72 hours of life. Rather than withdrawal, this syndrome is thought to be associated with the drug's direct effect and symptom resolution correlates with drug excretion.

It is important to note that not all NAS is a result of illicit or recreational drug use. As women delay having children to a later stage of life, more women are getting pregnant while dealing with chronic medical conditions. Infants born to women who are taking prescribed opiates for chronic pain conditions may develop NAS and, therefore, need to be observed.

Opiate maintenance therapy (particularly methadone) is associated with more frequent and more severe withdrawal in the neonate than active drug abuse or illicit drug use.[8] Maintenance therapy is preferred in pregnant women because it stabilizes the mother's lifestyle, reduces risk-taking behavior, and decreases the incidence of preterm birth and intrauterine growth restriction. Buprenorphine use for opiate addiction management in pregnancy has been associated with less severe NAS and decreased overall treatment dose in the infant than methadone but may not be an acceptable alternative for all substance abusers.[8-11] Women in opiate maintenance therapy should not attempt to wean from their medication during pregnancy.[12] Contrarily, they often require dose increases as their pregnancy progresses.

Screening and Scoring

Different tools can be used for screening for maternal substance abuse. Testing of the newborn's urine is of use only when collected in the early post-delivery hours. Meconium, the first stool passed by a newborn, is a good source for screening and gives a broader picture of exposure throughout the later stages of pregnancy. Hair and umbilical cord can also be used for screening. One should pay close attention to what is screened for at the institution as these tests have different panels associated with them. Be aware that opiate screens look only for natural opiates such as morphine, codeine, and heroin. Exposure to methadone, a synthetic opiate, can lead to a negative opiate screen. Methadone and other synthetic opiates (e.g., oxycodone) must be tested for specifically in order to capture them.

Symptoms of NAS can be categorized as respiratory, gastrointestinal (GI), or central nervous system (CNS) symptoms.[4,6,7] *Respiratory symptoms* include tachypnea, sneezing, nasal flaring, and nasal stuffiness. *GI symptoms*

include excessive sucking, poor feeding, regurgitation, and watery diarrhea. *CNS symptoms* include excessive high-pitched cry, sleep disturbance, tremors, increased tone, and convulsions. Following treatment and/or hospital discharge, subclinical symptoms may persist for weeks or months.

Several tools are available for scoring NAS symptoms.[7] The modified Finnegan tool is the most commonly used scoring system (Figure 5-1). Other commonly used tools include the Lipsitz and Neonatal Withdrawal Inventory. These tools assign a symptom-based score that is used to determine treatment initiation, titration, and weaning.

Each tool has its own trigger point for treatment. With the modified Finnegan tool, scores of eight are considered an indication for treatment. Institutions take different approaches to interpreting this number. Some institutions use the average of three scores, some look for two of three scores to be greater than eight, and others need two consecutive scores greater than or equal to eight to initiate pharmacologic treatment. Dose is titrated and weaned based on these scores.

Treatment

All babies at risk for NAS should be treated with non-pharmacologic measures, including swaddling them in a light blanket; dimming lights; stimulating them minimally; holding them skin-to-skin with parents (also known as kangaroo care); covering their hands to protect skin; changing their diapers frequently; offering them a pacifier; and breastfeeding (if mother is a candidate).[4,7]

Opiate Therapy

Opiate therapy is recommended for NAS treatment.[4,7] Either morphine or methadone may be used. Doses of various ranges have been used and include both weight-based as well as symptom-based dosing approaches. To date no head-to-head studies comparing the two treatment approaches have been published; however, this is currently an area of focus in neonatal medicine. Although AAP does not recommend a specific agent for the management of NAS, it recommends that each hospital develop a protocol to standardize the treatment approach.[7]

Phenobarbital

Phenobarbital is no longer recommended for first-line treatment, but it may have a place as an adjunct in some babies.[4,7,13] Adjunctive therapy may be

NEONATAL ABSTINENCE SCORING SYSTEM

System	Signs and Symptoms	Score	AM					PM					Comments
Central Nervous System Disturbances	Excessive high-pitched (or other) cry Continuous high-pitched (or other) cry	2 3											Daily Weight:
	Sleeps < 1 hour after feeding Sleeps < 2 hours after feeding Sleeps < 3 hours after feeding	3 2 1											
	Hyperactive Moro reflex Markedly hyperactive Moro reflex	2 3											
	Mild tremors disturbed Moderate-severe tremors disturbed	1 2											
	Mild tremors undisturbed Moderate-severe tremors undisturbed	3 4											
	Increased muscle tone	2											
	Excoriation (specific area)	1											
	Myoclonic jerks	3											
	Generalized convulsions	5											
Metabolic/ Vasomotor/ Respiratory Disturbances	Sweating	1											
	Fever <101 (99–100.8 F, 37.2–38.2 C) Fever > 101(38.4 C and higher)	1 2											
	Frequent yawning (> 3–4 times/interval)	1											
	Mottling	1											
	Nasal stuffiness	1											
	Sneezing (> 3–4 times/interval)	1											
	Nasal flaring	2											
	Respiratory rate > 60/min Respiratory rate > 60/min with retractions	1 2											
Gastrointestinal Disturbances	Excessive sucking	1											
	Poor feeding	2											
	Regurgitation Projectile vomiting	2 3											
	Loose stools Watery stools	2 3											
		Total Score											
		Initials of Scorer											

Figure 5-1. Modified Finnegan Scoring Tool

Source: Used with permission from Finnegan LP. Neonatal abstinence syndrome: assessment and pharmacotherapy. In: Nelson N, ed. *Current Therapy in Neonatal-Perinatal Medicine.* 2nd ed. Ontario, Canada: BC Decker; 1990:317. Copyright© Elsevier.

warranted when initial treatment has escalated to inducing side effects without managing the NAS symptoms. Any adjunctive treatment that is added also needs to be weaned and, therefore, should be used judiciously.

Clonidine

Clonidine has demonstrated efficacy in treating NAS and may also reduce the duration of pharmacologic treatment.[14-15] Clonidine affects the part of the brain that responds to the excessive norepinephrine released during withdrawal.[16] Based on its mechanism of action, it would be expected to treat the CNS effects of NAS but not the GI effects. It has the potential advantage of being safer than opiate replacement from a neurodevelopmental standpoint. The average dose used for NAS is 1 mcg/kg/dose every 4 hours.[14] Monitoring blood pressure and heart rate during treatment should be considered.

Buprenorphine

Buprenorphine is under investigation as an alternative treatment for NAS. Interestingly, the pilot study that was conducted to assess its use in NAS was also the first study in neonates to use the sublingual route of administration.[17]

Possible Adverse Effects

Adverse effects of opiates in neonates who have been exposed in utero are uncommon. Due to their tolerance, they do not often experience respiratory depression unless large doses are given. Occasionally, urinary retention becomes the dose-limiting effect.

Treatment should be assessed daily and weaned as often as every 48 hours if scores are stable and less than eight. Neonatal abstinence scores consistently in the zero to one range and/or a baby who will not wake up to eat are indications that he or she is overmedicated and the dose should be decreased, regardless of the wean schedule. Babies who have completed treatment with replacement opiate are generally observed for 48 hours prior to discharge to ensure that no rebound withdrawal requiring treatment is going to occur.

Breastfeeding

Mothers who are compliant with their sobriety program should be encouraged to breastfeed their infant.[7] Aside from the multitude of benefits that breastfeeding offers the mother/infant dyad, there are specific advantages for babies suffering from NAS. Babies with NAS who have received their mother's

breast milk have a decreased need for pharmacological treatment and a shorter treatment duration.[18,19] Breastfeeding is soothing and comforting to infants and probably accounts for a part of this benefit, but some babies included in these studies also received expressed breast milk from a bottle. The amount of methadone in breast milk is less than 3% of the maternal dose.[20] Even though it is a very small amount, this milk may help to ameliorate symptoms of NAS. Breast milk has the added advantage of being more easily digested and likely helps with the feeding intolerance that NAS babies experience. Mothers should be counseled that abrupt discontinuation of breastfeeding can lead to withdrawal, possibly requiring hospital admission and pharmacologic treatment.[21] The Academy of Breastfeeding Medicine has published guidelines advising which mothers are candidates to breastfeed their babies.[22]

Family Considerations

The social aspect of NAS can be complex. It is important for everyone working with these families to understand that addiction is a disease process and not a moral failure.[23] The American College of Obstetricians and Gynecologists states that "Addiction is a chronic, relapsing biological and behavioral disorder with genetic components. The disease of substance addiction is subject to medical and behavioral management in the same fashion as hypertension and diabetes."[24] Taking this statement into consideration while assisting in NAS management will create a better environment for the baby as well as the parents.

Conclusion

NAS management is an area where pharmacists can play an important role. Pharmacists should look for opportunities to get involved in the development of protocols and to advocate for breastfeeding in appropriate candidates within their institutions.

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Suggested Readings

Hudak ML, Tan RC; Committee on Drugs, Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. AAP Policy Statement on NAS. *Pediatrics.* 2012;129(2):e540-60.

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