Neonatal Abstinence Syndrome

AUTHOR: Prabhakar Kocherlakota, MD

Division of Neonatology, Department of Pediatrics, Maria Fareri Children's Hospital at New York Medical College, Valhalla, New York

KEY WORDS

benzodiazepines, breastfeeding, buprenorphine, Finnegan scores, inhalants, methadone, methamphetamine, morphine, neonatal abstinence syndrome, opioid abuse, opioid receptors, prescription opioids, selective serotonin reuptake inhibitor, withdrawal

ABBREVIATIONS

NAS—neonatal abstinence syndrome
SNRI—selective norepinephrine reuptake inhibitor
SSRI—selective serotonin reuptake inhibitor
TCA—tricyclic antidepressant

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Address correspondence to Prabhakar Kocherlakota, MD, Elaine Kaplan NICU, St Lukes Cornwall Hospital, 70 Dubois St, Newburgh, NY 12550. E-mail: pkocherlaj@aol.com

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abstract

Neonatal abstinence syndrome (NAS) is a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy. Withdrawal from licit or illicit substances is becoming more common among neonates in both developed and developing countries. NAS continues to be an important clinical entity throughout much of the world. NAS leads to a constellation of signs and symptoms involving multiple systems. The pathophysiology of NAS is not completely understood. Urine or meconium confirmation may assist the diagnosis and management of NAS. The Finnegan scoring system is commonly used to assess the severity of NAS; scoring can be helpful for initiating, monitoring, and terminating treatment in neonates. Nonpharmacological care is the initial treatment option, and pharmacological treatment is required if an improvement is not observed after nonpharmacological measures or if the infant develops severe withdrawal. Morphine is the most commonly used drug in the treatment of NAS secondary to opioids. An algorithmic approach to the management of infants with NAS is suggested. Breastfeeding is not contraindicated in NAS, unless the mother is taking street drugs, is involved in polydrug abuse, or is infected with HIV. Future studies are required to assess the long-term effects of NAS on children after prenatal exposure. *Pediatrics* 2014;134:e547–e561

Neonatal abstinence syndrome (NAS) is a clinical diagnosis, and a consequence of the abrupt discontinuation of chronic fetal exposure to substances that were used or abused by the mother during pregnancy. NAS is a generalized multisystem disorder, which predominantly involves the central and autonomic nervous systems, as well as the gastrointestinal tract. Neonatal withdrawal due to prolonged maternal opioid use may be severe and intense. Although NAS is rarely fatal, it can cause significant illness and often results in prolonged hospital stays. This review provides a summary of the history, epidemiology, pathophysiology, clinical presentation, toxicology confirmation, and treatment of NAS. Implications for breastfeeding and follow-up are discussed.

HISTORICAL BACKGROUND

Although opium use dates back to the ancient civilizations of Mesopotamia (~3400 BCE), the first surviving records of opium addiction date from the end of the 18th century.[1] Morphine was isolated in 1804, heroin was synthesized in 1874, and addiction to these opioids became more common after their commercial production.[2] An increase in the incidence of morphine and heroin addiction among women was noted as early as the 19th century[3]; however, infants were not thought to be affected because it was believed that morphine use among women was associated with sterility and a loss of sexual desire. That fallacy was corrected after the first reported case in a neonate (1875),[4] who manifested signs of opioid withdrawal at birth, diagnosed with congenital morphinism. Subsequently, there was a surge of similar reports.[5] However, most of the involved infants died and no specific treatment was offered,[6] until ~1903, when a report appeared in medical literature that described the survival of a neonate after morphine treatment.[7] Congenital morphinism remained a medical curiosity until 1947, when the successful treatment of seizures in an infant with congenital morphinism was reported.[8] Thereafter, increased reports of congenital morphinism (and related morbidity and mortality) resulted in significant attention from obstetricians as well as pediatricians.[9,10] Congenital morphinism was subsequently renamed as abstinence syndrome in neonates.

Methadone was introduced as a replacement treatment of opioid addiction in 1964.[11] Methadone use during pregnancy was at first believed to be unassociated with withdrawal in neonates; however, subsequent experience contradicted this initial misimpression.[12] Buprenorphine was approved as an alternative to methadone for opioid addiction in both Europe (1996) and the United States (2002).[13,14] The use of buprenorphine during pregnancy has also resulted in NAS.[15,16] Neonatal withdrawal secondary to the maternal use of prescription pain medications is the latest additional etiology in the history of neonatal withdrawal (Fig 1).[17,18]

INCIDENCE

The incidence of NAS has been increasing in the United States[18] and elsewhere.[19] The Substance Abuse Mental Health Services Administration reported that 1.1% of pregnant women abused opioids (0.9% used opioid pain relievers and 0.2% used heroin) in 2011.[20] In a recent national study, maternal opioid use was shown to have increased from 1.2 mothers per 1000 live births in 2000 to 5.6 mothers per 1000 live births in 2009, and diagnoses of NAS correspondingly increased from 1.2 to 3.4 per 1000 live births.[18] In a study from Florida, the number of neonates who had NAS and were admitted to the NICU increased by 10-fold from 2005 to 2011.[21] Increases in the incidence of NAS have been reported uniformly across community hospitals, teaching hospitals, and children's hospitals.[22] All communities and all ethnicities have been affected.[20,23]

GROWING EPIDEMIOLOGY

Although heroin abuse has remained relatively constant in developed countries, it has increased alarmingly in developing countries.[24,25] Heroin abuse is more common among mothers who are unmarried, unemployed, less educated, and less insured. Pregnancies among heroin-abusing women are usually unplanned and with minimal prenatal care. These mothers generally lead risky lifestyles, and often have multiple social, nutritional, physical, and mental health problems.[26] Infants born to these mothers usually are premature, usually have low birth weights, and are often growth restricted. Many of the infants born to heroin-abusing mothers develop NAS immediately after birth.[27]

Methadone, a synthetic complete μ-opioid receptor agonist, has become the standard of care for pregnant women with opioid addiction. Methadone maintenance treatment during pregnancy optimized obstetric care, decreased illicit drug use, and improved fetal outcomes.[28] Nevertheless, methadone treatment also has been related to the increased incidence of NAS.[12,29] Research on the pharmacokinetics of methadone during pregnancy has led to the administration of higher methadone doses than were used 20 years ago[30,31]; however, it is unclear if these increases in maternal methadone dose have further increased the incidence of NAS.[32–37]

Buprenorphine, a semisynthetic partial μ-opioid receptor agonist and a complete κ-opioid receptor antagonist, has been found to be equally safe and efficacious and has become an effective

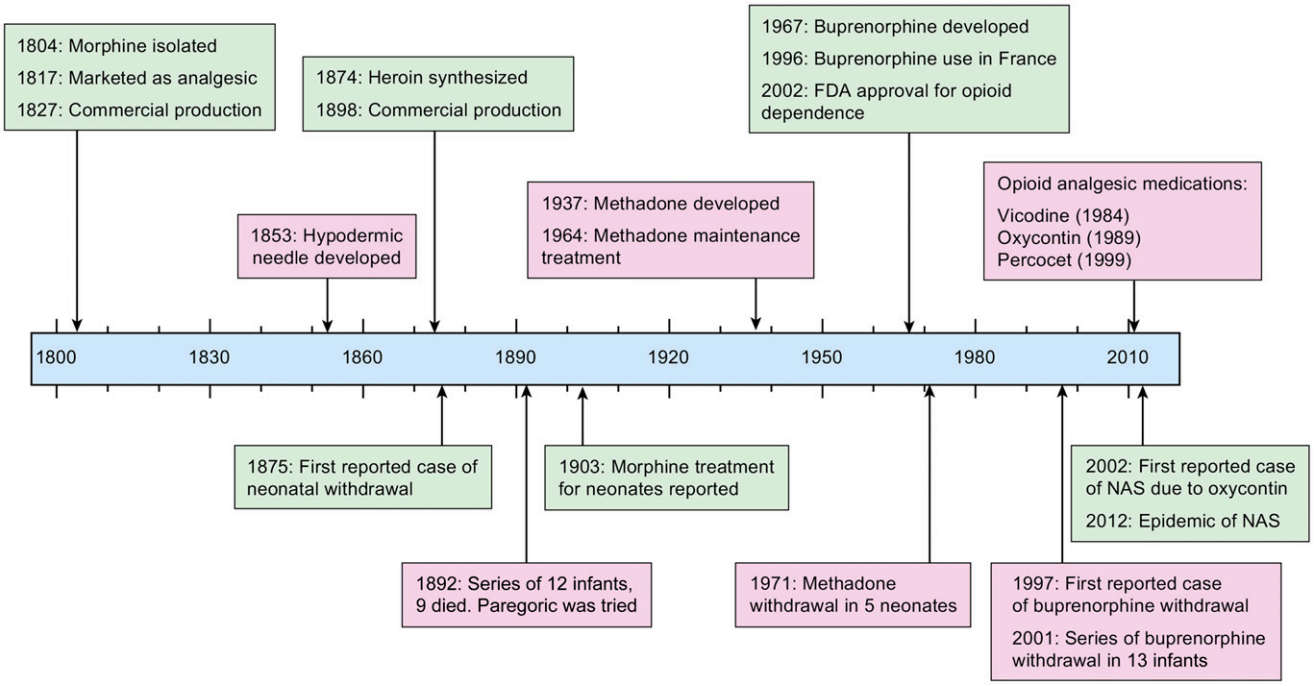

FIGURE 1
Time line of NAS. FDA, Food and Drug Administration.

alternative to methadone for opioid dependency during pregnancy.[38–40] Multiple studies demonstrated that buprenorphine maintenance treatment in pregnancy is either comparable or superior to methadone treatment with regard to NAS; however, these studies were observational, retrospective, or small (Supplemental Table 5).[41–48] A larger prospective randomized study favored buprenorphine over methadone with regard to the doses and durations of morphine treatment and lengths of hospital stays, but not the incidence nor the severity of NAS.[49] A recent meta-analysis did not favor one over the other.[50] No relationship has been found between maternal opioid dose and NAS.[51] Neither methadone nor buprenorphine were approved for use in pregnancy.

The abuse of prescription pain medications has increased among pregnant women.[52–55] A recent study reported that 6% of mothers used opioids for more than a month during pregnancy.[56] Another study reported that the incidence of oxycodone abuse among pregnant women doubled within the 18-month study period.[57] Multiple recent studies have noted increases in the incidence of NAS secondary to prescription drug abuse.[58–60]

The use of psychotropic medications to control depression and anxiety during pregnancy has increased over the past decade.[61,62] Approximately 1.8% of pregnant mothers use antidepressants and 3.0% use benzodiazepines.[63,64] Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines are associated with NAS.[61,64] Women with mental health disorders are also at increased risk of substance abuse.

As of 2012, >4% of pregnant women have used nonopioid illicit substances during pregnancy as compared with <3% in 2002.[65] Although the use of methamphetamines and inhalants decreased during the same period in North America and Europe, the use of methamphetamines and inhalants is an increasing concern in developing countries.[66–68] Both of these substances also are associated with NAS.[69,70]

The spectrum of NAS has changed over time. Before 1970, NAS was generally secondary to either morphine or heroin use. Today, NAS may be secondary to the use of morphine, heroin, methadone buprenorphine, prescription opioid analgesics, antidepressants, anxiolytics, and/or other substances. This spectrum of causes has worsened, not only because of an increase in the use of opioids but also because of the simultaneous use of multiple opioids, which is further complicated by the concurrent use of multiple other licit and illicit substances. Accordingly, NAS has become more common and more complex, imposing additional social, economic, and health care costs on society.[18,60]

PATHOPHYSIOLOGY

The pathophysiological mechanism of opioid withdrawal in neonates is not known. Several factors can affect the

accumulation of opioids in the fetus. Opiate drugs have low molecular weights, are water soluble, and are lipophilic substances; hence, they are easily transferable across the placenta to the fetus. The transmission of opioids across the placenta increases as gestation increases.[71] Synthetic opiates cross the placenta more easily compared with semisynthetic opiates.[72] The combination of cocaine or heroin with methadone further increases the permeability of methadone across the placenta.[73] Together, the ease with which these drugs can cross the blood-brain barrier of the fetus, and the prolonged half-life of these drugs in the fetus,[74] may worsen the withdrawal in infants. Neonatal abstinence syndrome is the end result of the sudden discontinuation of prolonged fetal exposure to opioids.

Opioid withdrawal is a complex biological phenomenon. The cellular and molecular mechanisms of this process are poorly understood even in adults. The pathophysiology of opioid withdrawal is more complex in neonates as a result of immature neurologic development, impaired neurologic processing, and complex materno-feto-placental pharmacokinetics.

Opioids mostly act through opioid receptors (G protein–coupled receptors, μ, κ, and δ), which are extensively distributed across the central nervous system and are also located within the peripheral nervous system, gastrointestinal system, and various other systems.[75] The density and affinity of μ-receptors in neonates are as good as those in adults; however, evidence failed to show similar development of κ- and δ-receptors, as well as other receptors, in the neonatal brain.[76] A lack of opioids in a chronically stimulated state increases activity in the opioid receptors, leading to increased adenyl cyclase activity, and cellular ionic imbalance. Ultimately, this results in the increased production of various neurotransmitters through a cascade of enzymatic activities (Fig 2).[77]

The most important center of activity in opioid withdrawal is the locus coeruleus of the pons. This is the principal noradrenergic nucleus of the brain and is extremely sensitive to opioid status.[78] A lack of opioids causes increased production of norepinephrine,[79] which is responsible for most of the signs of NAS. The ventral tegmental area of the midbrain, the storage center of dopamine, releases decreased dopamine during opioid withdrawal.[80,81] Opioid withdrawal also causes decreased serotonin expression in the dorsal raphe nucleus,[82,83] causing sleep disturbances in neonates undergoing opioid withdrawal. Opioid deficits also affect the functioning of the autonomic and peripheral nervous systems, as well as the gastrointestinal system. Opioid deficits cause increased production of multiple neurotransmitters, such as acetylcholine, during withdrawal phase.[84] Opioid withdrawal may activate the hypothalamic-pituitary-adrenocortical axis, leading to increased corticotrophin release.[85] Further, opioid withdrawal may be associated with hyperalgesia.[86] It also may affect gene expression within various body systems (Fig 2).[87]

The incidence and severity of withdrawal is less extensive in preterm neonates.[88] Various factors explain the decreased incidence in preterm neonates, including decreased cumulative exposure,[88] decreased transmission across the placenta during early gestation,[71] decreased morphine clearance,[89] decreased excretion because of immaturity of the kidneys and liver, decreased fatty tissues in preterm infants (methadone is accumulated in fatty tissue), decreased receptor development, and decreased receptor sensitivity.[76,90]

Withdrawal symptoms among neonates whose mothers took an SSRI or SNRI may result from excess serotonin and noradrenaline. Neonatal withdrawal from TCA is a cholinergic rebound phenomenon. Neonatal withdrawal with benzodiazepines probably results from the increased release of γ-amino butyric acid.[91] Methamphetamine withdrawal may be secondary to a decrease in dopamine, serotonin, and other monoamines.[92] Inhalant withdrawal involves the dopamine, glutamate, and γ-amino butyric acid pathways.[68]

CLINICAL PRESENTATION

NAS continues to be an important clinical entity and leads to a constellation of signs and symptoms that involve multiple systems. At presentation, signs of NAS usually include tremors, irritability, excessive crying, and diarrhea. Occasionally, seizures also are present. Central nervous system signs, including irritability, jitteriness, tremors, and excessive crying, usually appear first. Hyperirritability, which is a hallmark of this syndrome, can lead to agitation, difficulty sleeping, and inconsolable crying. The high-pitched, uncontrollable excessive crying is often striking, and requires immediate attention.

Tremors, exaggerated Moro reflex, hypertonia, and myoclonic jerks are more common during methadone withdrawal.[93] These can mimic seizures, and an EEG may be required for confirmation. Seizures are observed in 2% to 11% of neonates with NAS, are a serious manifestation of withdrawal, and should be treated immediately.[94] The exact cause of withdrawal-related seizure is unknown, although the threshold for seizure activity may be decreased due to upregulation of sodium channels as a result of receptor instability.[75] Heart rate, respiratory rate, muscle tone, and other physiologic responses to stimuli are impaired in these neonates with NAS as a result of the dysregulation and instability of the autonomic nervous

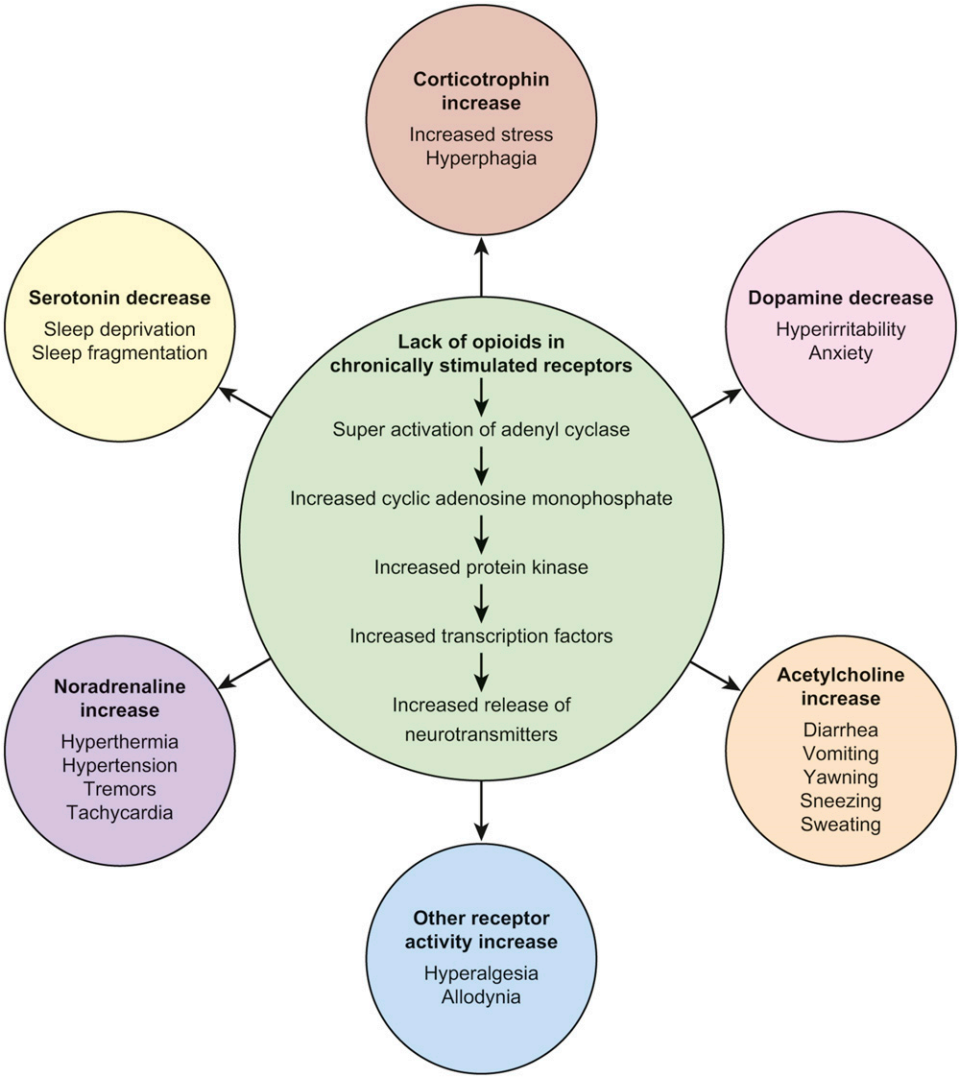

FIGURE 2

A schematic illustration of the mechanism of opioid withdrawal in neonates. Lack of opiates in a chronically stimulated state leads to the upregulation of cyclic adenosine monophosphate, which leads to increased production and release of various neurotransmitters through complex mechanisms. Withdrawal is the result of increased production of noradrenaline, acetyl choline, corticotrophin, and other substances, as well as the decreased production of serotonin and dopamine. These mechanisms may be able to explain most of the signs that are characteristically seen in neonates with abstinence syndrome.

system.[95] Other autonomic nervous system signs include temperature instability, sweating, sneezing, and mottling. These may persist for months, or even longer, especially in cases involving maternal buprenorphine use.[93] A chemical odor is common in neonates born to mothers who abuse inhalants.[70]

Tachypnea, nasal flaring, and nasal stuffiness may be misinterpreted as respiratory distress in newborns. Hyperthermia, although rarely higher than 102°F, can result in misdiagnosis as sepsis. Poor feeding, excessive motor activity, regurgitation, vomiting, and diarrhea may lead to poor weight gain in these infants. Severe diarrhea, leading to dehydration and electrolyte imbalance, is more commonly observed in heroin withdrawal. Perianal skin excoriation secondary to excessive loose stools further increases irritability and agitation. Similarly, irritability and agitation may be increased by unattended skin excoriation over the face and body, which are secondary to excessive motor movements. Hyperphagia is widely recognized in infants with NAS, who may require intake of more than 150 calories per kilogram per day.[96]

The onset, duration, and severity of NAS depend on several characteristics of the drugs abused by the mother, including their types, amounts, half-lives, receptor-binding capacities, receptor affinities, placental transferability, and other pharmacological properties. Additionally, NAS may be affected by the time of the last dose, the duration of exposure, the total accumulation of the exposure, and the multiplicity of the

substances that the neonate was exposed to.[97–99]

Of the opioids, heroin exposure causes earlier and shorter withdrawal, whereas methadone and buprenorphine exposure lead to later onset and longer withdrawal. Of the nonopioids, methamphetamines cause immediate withdrawal, psychotropic medications usually induce transitional and self-limiting withdrawal, and the results are indeterminate for benzodizepines.[96–100] Table 1 summarizes the onset, duration, and frequency of NAS caused by various substances.

Onset may be delayed with buprenorphine, especially in higher doses.[102,103] Delayed onset also is noted when opioids are used along with barbiturates or benzodiazepines.[104] In general, infants born at term, infants with good birth weight, polydrug-exposed neonates, and infants with delayed drug metabolism are more prone to severe and prolonged withdrawal. Additional risk factors for increased NAS may include maternal smoking, methadone usage, and male gender. Increased length of hospital stays and an increased need for pharmacotherapy in NAS have recently been observed among neonates with the μ-opioid receptor (*OPRM1*) gene and the catechol-O-methyltransferase (*COMT*) gene. However, these results need to be explored further for clinical application.[105] Risk factors associated with severity and intensity are summarized in Table 2.

NAS may involve an initial phase that is short but intense, consisting of tremors, seizures, irritability, feeding problems, vomiting, diarrhea, hyperthermia, and other systemic signs (lasting for 1 to 2 weeks). This initial phase may be followed by a long chronic and relapsing course that includes hyperirritability, sleep disturbances, hyperphagia, and other neurologic and autonomic signs (lasting for a few weeks to a few months).

TOXICOLOGY CONFIRMATION

Although NAS is a clinical diagnosis, toxicological confirmation is necessary to identify the exact type of substance that the mother was using or abusing and to confirm or rule out the use of other licit or illicit substances during pregnancy. Analysis of the urine or meconium, which is the matrix of choice for detecting in-utero drug exposure, is a noninvasive, inexpensive, reproducible, and fully automated procedure; specimen collection also is relatively easy in neonates. The analysis can be performed by using the immunoassay technique in hospital clinical laboratories, by using specific lower cutoff concentrations for each drug.[116] Because these are merely screening tests, confirmation is required from secondary testing with mass spectrometry after the chromatographic method, especially if quantitative or definitive results are needed. However, these tests are expensive and time-consuming, and require significant expertise.

TABLE 1 Onset, Duration, and Frequency of NAS Caused by Various Substances

Drug	Onset, h	Frequency, %	Duration, d
Opioids			
Heroin	24–48	40–80[27]	8–10
Methadone	48–72	13–94[37]	Up to 30 or more
Buprenorphine	36–60	22–67[46,48]	Up to 28 or more
Prescription opioid medications	36–72	5–20[56,60]	10–30
Nonopioids			
SSRIs	24–48	20–30[64]	2–6
TCAs	24–48	20–50[64]	2–6
Methamphetamines	24	2–49[101]	7–10
Inhalants	24–48	48[70]	2–7

Meconium testing is more sensitive than urine testing, and has a longer window of detection (from 20 weeks of gestational age); however, the extraction of the drug depends on the solvent. Urine testing is more popular. It has a shorter window for detection (a few days), but extraction is efficient (Table 3).[116,117] Detection of the abused drug depends on the amount and the duration of drug exposure, the method of maternal administration, and the individual metabolism and clearance of the drug in the mother and her fetus. Although natural opioids are easily detectable in urine and meconium, semisynthetic and synthetic opioid drugs are not.[118,119] Synthetic cannabinoids, synthetic cathinones, and other designer drugs cannot be detected with regular laboratory tests and may require more selective methods.[121,122]

False-positive results are often seen with amphetamines. False-positive results are observed when meconium is contaminated with urine, and also when soap or alcohol has been used for cleaning before collection.[116] False-negative results can occur with urine because of delays in collection. Additionally, urine is relatively dilute at birth in neonates. Meconium analysis may yield false-negative results for marijuana.[117] Improper storage of meconium may interfere with analysis because meconium is light-sensitive and temperature-sensitive. A combination of maternal urine and neonatal meconium usually yields the best results. Peripartum use of opioids for maternal analgesia may interfere with neonatal toxicology results. Hair and umbilical cord analyses may help detect even minor and remote exposures; however, such tests require reference laboratories. Early detection of substance exposure leads to early assessment and management of the affected neonate.[124] Inaccurate and delayed detection may not only delay

TABLE 2 Risk Factors for Increasing Severity and/or Intensity of NAS

Definite	Probable
Term[97,98,108]	Male gender[112,113]
Good birth weight[97,109]	Methadone[45,46]
Polydrug abuse[106,107, 110]	Smoking[97,109,114]
Combination with benzodiazepines[97,111]	Combination with SSRIs[97,109,115]
μ-opioid receptor (OPRM1 118 AA) positive[105]	
Catechol-O-methyltransferase (COMT 158 AA) positive[105]	

treatment, but also may create conflicts with and within the family.

MANAGEMENT

Many scoring systems allow clinicians to assess the severity of NAS, but no scoring system is perfect and all the systems are subject to a strong interobserver variability. At present, the modified Finnegan scores remains the most common tool that is used.[126,127] The Finnegan scoring system is used for opioid and nonopioid withdrawal assessment.[70,96] Shortened or simplified versions of these scores have met with little success.[128,129] Quantifying the severity of NAS assists in determining if and when pharmacological intervention will be needed. Scoring also assists in monitoring, titrating, and terminating therapy.[130] Scoring should be performed after feeds, at 3- to 4-hour intervals, when the infant is awake. The score should represent the status of the infant both at the time of assessment, and during the preceding time period. These scoring systems are generally useful for term neonates, but not for preterm infants.

NONPHARMACOLOGICAL CARE

Management of the neonate includes both pharmacological and nonpharmacological care. Nonpharmacological therapy is the first option in all cases, and may suffice in cases of mild withdrawal. Nonpharmacological therapy is easily acceptable, less expensive, and less controversial. Nonpharmacological therapy can be attempted in all infants before initiating pharmacological therapy. Successful management comprises gentle handling, demand feeding, and careful avoidance of waking the sleeping infant. Swaddling lessens stimulation, decreases crying times, and promotes sleep that is more sustained.[131,132] Continuous minimal stimulation practices with dim light and low noise must be implemented in all neonates. Frequent feeds, high-calorie formula, and thickened feeds may meet nutritional and metabolic demands. Kangaroo care and pacifiers may help to calm infants. Water beds also may help but not rocking beds.[133] Music therapy and massage therapy may soothe some infants.[134] Noninsertive acupuncture also has been attempted.[135] Holding, cuddling, and manual rocking also can help. All infants need to be monitored for feeding, weight gain, and good sleep.[96] To date, no studies have compared the effectiveness of any of these measures in neonates with NAS. To control the severity of withdrawal, it may be especially important to stay alert early to signs of the newborn's irritability. If parents, volunteers, and cuddlers are immediately available, they can calm and soothe these infants before the cycle of irritability, excessive crying, poor feeding, and lack of sleep sets in. Rooming-in of mother and infant also decreases the severity of withdrawal.[136,137] A caring, nonjudgmental approach may encourage maternal participation. Active maternal participation is the best nonpharmacologic care. Continuous excellent supportive care can help to avoid pharmacological intervention, and also may lead to earlier discharge from hospital.

TABLE 3 Urinary Screening for Various Drugs and Approximate Duration of Detection in the Neonate[116,118–120]

Substance	Compound/Metabolite/Usage	Duration of Detectability
Alcohol[123]	Ethanol	Few h
	Fatty acid ethyl esters	Up to 5 d
	Ethyl glucuronide	Up to 30 h
	Ethyl sulfate	
Amphetamines	Amphetamine	1–2 d
	Methamphetamine	1–2 d
Barbiturate	Short acting	<2 d
	Long acting	1–7 d
Benzodiazepines	Short acting	1–7 d
	Long acting	Up to 30 d
Cocaine	Cocaine	6–8 h
	Metabolites	2–5 d
		(up to 10–22 d with heavy use)
Marijuana	Single use	1–3 d
	Moderate use	5–7 d
	Heavy	up to 10 d
	Chronic heavy use	up to 30 d
Opiates	Heroin, morphine, codeine	1–2 d
	Hydromorphone, oxycodone	2–4 d
	Methadone	2–3 d
	Methadone metabolite	Up to 6 d
	Buprenorphine[125]	2–3 d
	Buprenorphine	2–3 d
	Norbuprenorphine	
Phencyclidine		1 to 8 d

PHARMACOLOGICAL CARE

Medical intervention to control withdrawal symptoms is required in 27% to 91% of neonates with NAS.[138,139] However, because of the complex nature of withdrawal and the unknown effects of various licit and illicit drugs, there are currently no uniformly accepted pharmacological interventions or standardized regimens for the management of NAS.[96] Many available medications can facilitate short-term amelioration of the withdrawal symptoms; however, no large-scale studies have compared these medications because the spectrum of withdrawal varies for different drugs, doses, weights, and gestational periods. Medications are required only when (1) supportive therapy fails to control the signs and symptoms; (2) withdrawal scores remain high; (3) serious signs are observed, such as seizures; or (4) withdrawal is associated with severe dehydration because of diarrhea and/or vomiting. Delays in the administration of pharmacological therapy are associated with higher morbidity and longer hospital stays.[140]

Many medications are available to treat these signs, but no single medication is suitable for every patient and no single regimen is acceptable to every patient. The pharmacological management of NAS has been a subject of recent reviews.[141–143] Opioid antagonists, such as naloxone, are contraindicated because they may precipitate seizures in neonates. Older medications, such as paregoric or tincture of opium, are no longer used or available because they have toxic ingredients and high alcohol content. Sedatives, such as diazepam and chlorpromazine, are not useful because of their prolonged half-lives and associated complications.[144] The mechanisms of action, doses, advantages, and risks of commonly used medications for NAS are included in Table 4.

Morphine is the most commonly preferred medication.[127,145] Morphine decreases the incidence of seizures, improves feeding, eliminates diarrhea, decreases agitation, and can control severe symptoms.[146] However, morphine treatment also prolongs the length of hospital stay.[147] Incremental increase or decrease of the dose of morphine depending on the severity of withdrawal is often a common practice.[46,143] Because morphine has short half-life, it must be provided every 3 to 4 hours. Morphine solution is stable and easy to administer.[148] Additionally, morphine treatment is relatively safer and more suitable for NAS management.[149] Morphine dose can be escalated rapidly for higher scores; however, weaning has to be gradual. When an optimal response is not attained with the maximal dose, additional medications may be considered. An algorithmic approach (Fig 3) for the management of NAS is not only useful for consistent management, but is especially beneficial for community hospital settings, where most cases of NAS are managed.[22]

Methadone is an alternative to morphine for the treatment of NAS. Methadone is more frequently used in the United States than in other countries.[130,150] Methadone can be administered only twice per day; however, because of the long half-life of methadone, it may be difficult to titrate the methadone dose. The methadone dose also can be increased or decreased depending on the severity score. Caution must be exercised when methadone is used along with other medications, such as phenobarbital or antiretroviral medications.[151] Buprenorphine is a new option for the treatment of NAS and must be given sublingually; however, no large-scale studies are available to support the use of this medication.[152] Ideally, both methadone and buprenorphine are logical choices, if the mothers were receiving these medications prenatally.

Phenobarbital is a drug of choice for nonopiate NAS.[134,150] Although it is occasionally used as a single therapeutic agent for opioid NAS, phenobarbital is more often used as an adjunct to morphine or methadone.[130,144] Phenobarbital does not prevent seizures at the dosage administered for withdrawal, nor does it improve gastrointestinal symptoms. However, phenobarbital is advantageous because it can be used as an adjuvant, especially in infants suffering withdrawal from polydrug abuse,[145] which is generally severe and prolonged. Clonidine, a centrally acting α-adrenergic receptor agonist, has been studied as a single replacement therapy or adjunct therapy, although the theoretical risk of hypotension and bradycardia may always prohibit increasing its dose. No large-scale studies have proven the efficacy of clonidine for NAS.[153,154] Clonidine and phenobarbital levels can be monitored, and both are beneficial for decreasing the duration of treatment as well as for curtailing the use of higher doses of morphine or methadone.[138,155]

BREASTFEEDING

In 2001, the American Academy of Pediatrics removed the restrictions on breastfeeding for mothers on any dosage of methadone.[156] This position was further reaffirmed in 2013.[157] Multiple studies have validated the finding that breast milk contains only minimal quantities of methadone and buprenorphine.[158–160] Obstetricians and lactation specialists also have endorsed breastfeeding among opioid-addicted mothers.[161,162] Subsequent to these recommendations, some improvements in breastfeeding practices have been noted.[127,163] The amount of methadone or buprenorphine in breast milk is too small to treat NAS, and the

TABLE 4 Pharmacological Treatment Options for NAS

Medication	Mechanism of Action	Dose	Advantages	Disadvantages
Morphine	Natural μ-receptor agonist	0.05–0.2 mg/kg/dose q 3–4 h Increase by 0.05 mg/kg Maximum dose: 1.3 mg/kg/day[141]	No alcohol Short half-life (9 h)	Sedation Apnea Constipation Frequent dosing
Methadone	Synthetic complete μ-receptor agonist N-methyl-d-aspartate antagonist	0.05–0.1 mg/kg/dose q 12 h, increase by 0.05 mg/kg q 48 h Maximum dose: 1 mg/kg/d[21]	Long half-life (26 h) 12 hourly doses	Longer duration of treatment Alcohol 8% Frequent follow-up needed (Variable half-life)
Phenobarbital	γ-amino butyric acid agonist	Loading dose: 16 mg/kg Maintenance dose: 1–4 mg/kg/dose q12 h[150]	Long half-life (45–100 h) Monitor level	Possible hyperactivity High treatment failure Alcohol 15% Drug-drug interactions Sedation
Clonidine	α-adrenergic receptor agonist	Initial dose: 0.5–1 μg/kg, followed by 0.5–1.25 μg/kg per dose q 4–6 h[153]	Nonnarcotic antagonist No sedation No alcohol Long half-life (44–72 h) Monitor level	Hypotension Abrupt discontinuation may cause rapid rise of blood pressure and heart rate
Buprenorphine	Semi-synthetic partial μ-receptor agonist, κ-receptor antagonist	Dose: 4–5 μg/kg/dose q 8 h Maximum dose: 60 μg/kg/d[152]	Sublingual route Half-life (12 h)	Alcohol 30% Adjuvant medications required

q, every.

sudden discontinuation of breast milk is not associated with the worsening of NAS[164,165]; however, gradual weaning from breastfeeding is advised.[166] Because of the high concentrations of hydrocodone and oxycodone in breast milk as well as the reduced clearance of some of these medications in some neonates, mothers taking these prescription opioids should be alerted to the problem of sedation among infants when breastfeeding.[167–169] Breastfeeding increases mother-infant bonding, enhances maternal confidence, and encourages active maternal participation in the management of the infant. Breastfeeding may decrease the incidence of NAS,[170] the need for pharmacological treatment,[99,171] and the length of the hospital stay.[111,172] Breastfeeding is not contraindicated by psychotropic medications.[61] Breastfeeding is contraindicated only if the mother is taking illicit drugs, has polydrug abuse, or is infected with HIV.

DISCHARGE AND FOLLOW-UP

When the neonate shows no major signs of withdrawal and the infant is feeding well, sleeping well, gaining weight, and maintaining stable withdrawal scores with minimal medication support, the infant can be discharged with the parents (provided that the home environment is safe and stable) or to a foster home (if necessary). A multidisciplinary approach that includes parental participation is extremely helpful in the management of these neonates, not only during the hospital stay but also after discharge from the hospital. Indeed, these infants are more prone to both short-term and long-term problems.[173,174] Whether prenatal opioid exposure or postnatal opioid treatment has any long-term effects on the newborn brain is largely unknown. Indeed, no longitudinal follow-up studies have extended beyond the first few years of life.[175] Animal experiments have neither proven nor disproven the effects of chronic maternal opioid administration on dendritic growth and development in the fetus.[176,177] Recent observations of delayed or altered maturation of neuronal connective tracts and smaller neuroanatomic volumes in infants born to opioid-addicted mothers[178,179] have established an urgent need for studies of long-term outcomes in these children. No significant adverse long-term outcomes were reported among neonates who were exposed in utero to SSRIs, SNRIs, TCAs, benzodiazepines, or methamphetamines.[180–182]

During follow-up, infants with NAS particularly require (1) neurodevelopmental assessments to identify motor deficits, cognitive delays, or relative microcephaly[174,183]; (2) psycho-behavioral assessments to identify hyperactivity, impulsivity, and attention-deficit in preschool-aged children, as well as school absence, school failure, and other behavioral problems in school-aged children[184]; (3) ophthalmologic assessment to identify nystagmus, strabismus, refractive errors, and other visual defects[185–187]; (4) growth and nutritional assessment to identify failure to thrive and short stature[174]; and (5) family support assessments to exclude continuous maternal substance abuse and child abuse. Parents need to be educated about sudden infant deaths as well as complications due to perinatal infections. The complexity and challenging nature of the home

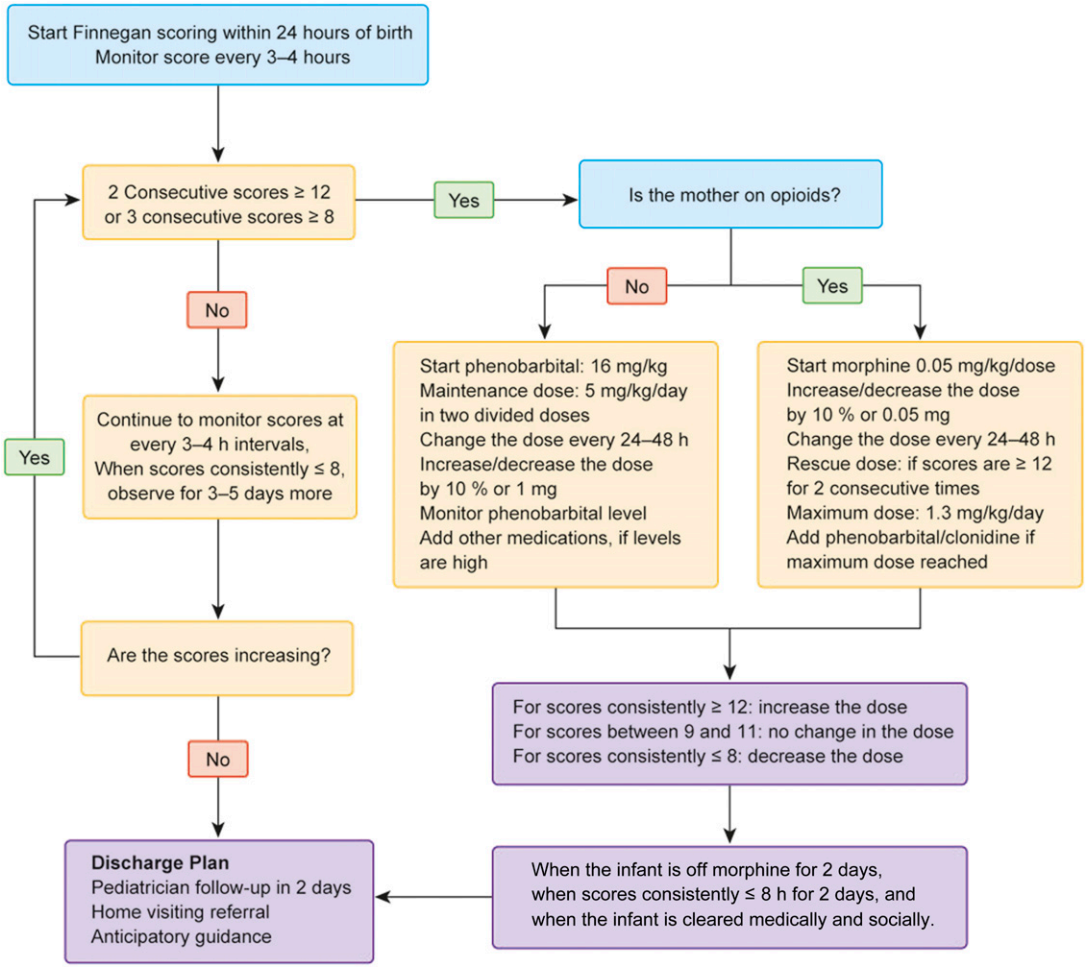

FIGURE 3

A management plan for NAS in neonates. Medications are to be initiated, increased, decreased, or discontinued depending on the Finnegan score. Morphine can be initiated at a higher dose if scores are high; for example, if the scores are 17 to 20, morphine can be started at 0.12 mg per dose, and if the scores are ≥25, morphine can be initiated at 0.20 mg per dose.[49] Morphine dose can also be escalated by >10% for higher scores.[21] Methadone can be substituted for morphine for opioid withdrawal. Cardiopulmonary monitoring of the infant is preferred during the acute stage.

atmosphere should never be underestimated in these situations. The importance of an optimal home environment for the global development of these children should be emphasized to all parents.

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