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

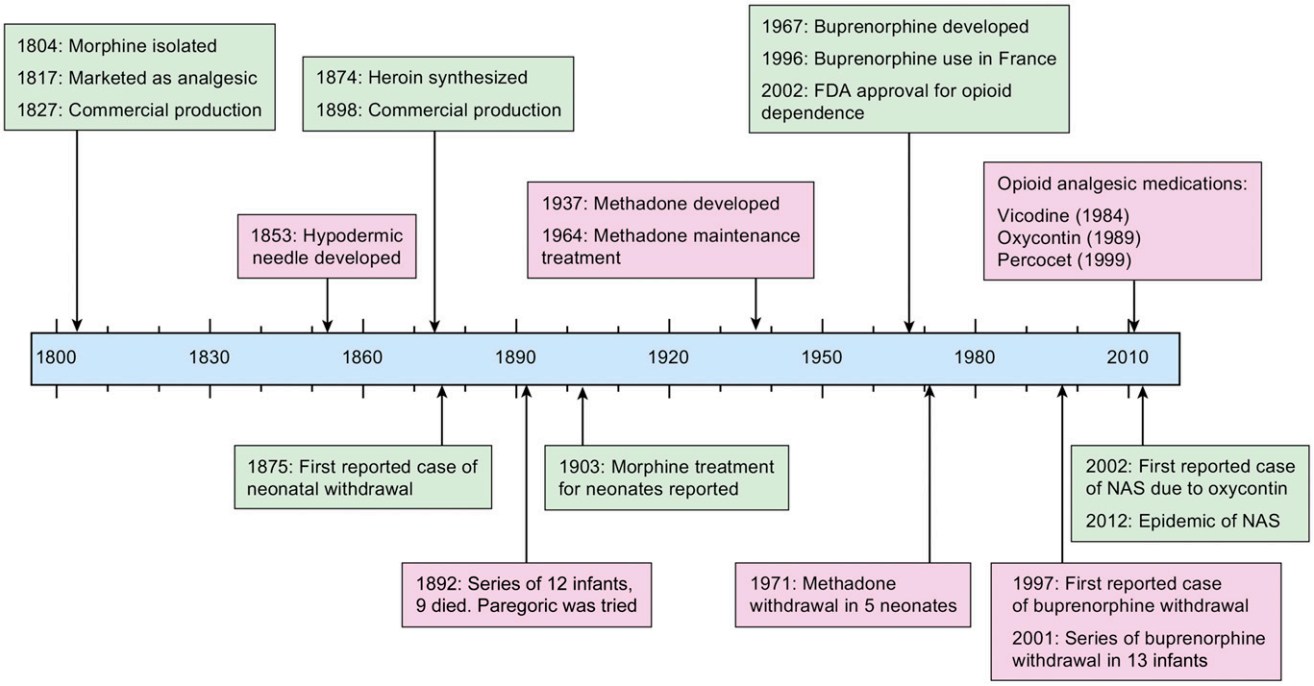

FIGURE 1
Time line of NAS. FDA, Food and Drug Administration.

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

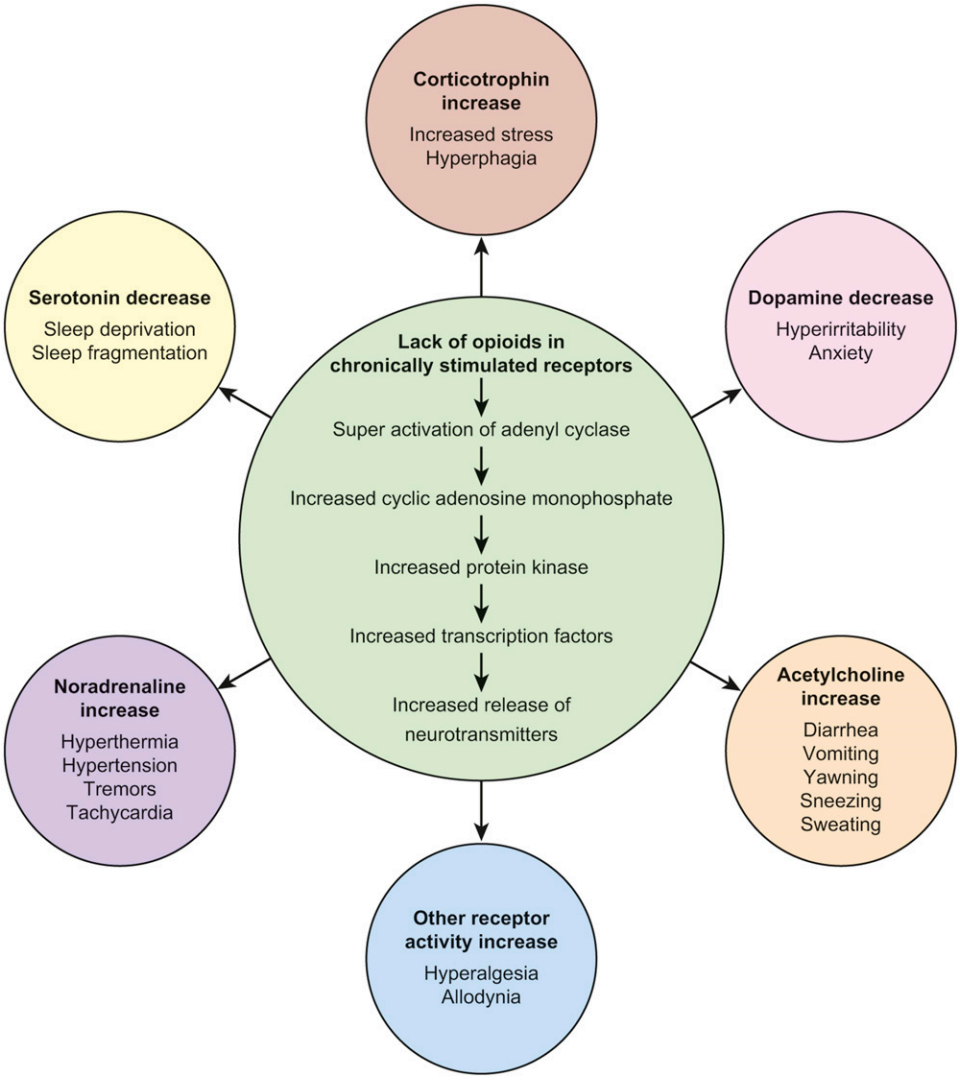

FIGURE 2

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

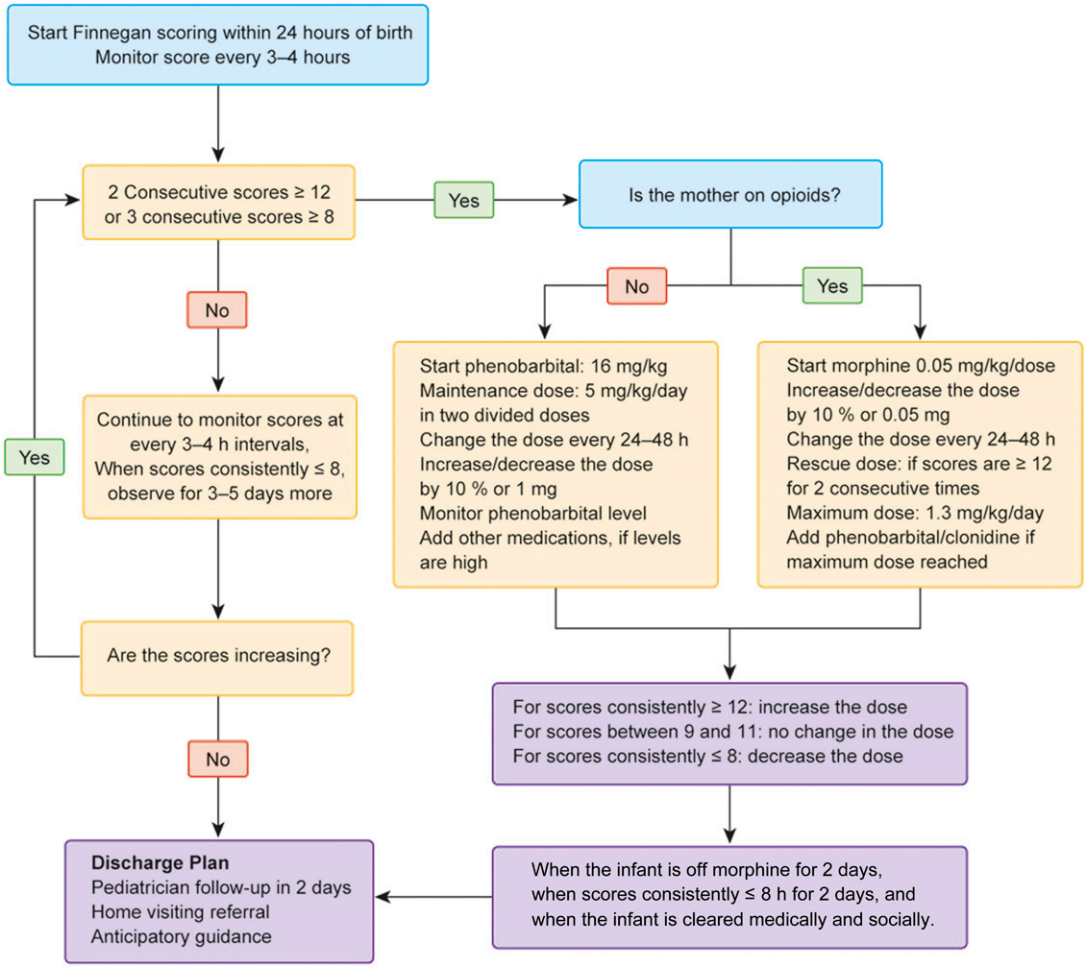

FIGURE 3

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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REFERENCES

1. Heroin timeline. Heroin addiction. Available at: www.heroinaddiction.com/heroin_timeline.html. Accessed October 12, 2013
2. Merry J. A social history of heroin addiction. *Br J Addict Alcohol Other Drugs*. 1975;70(3):307–310
3. Courtwright D. *Dark Paradise: Opiate Addiction in America Before 1940*. Cambridge, MA: Harvard University Press; 1982
4. Menninger-Lerchenthal E. Die morphin kranheit der neugeborenen morphine stischer mutter Monatsschr. *F Kinderh*. 1934;60:182–193
5. Happel TJ. Morphinism in its relation to the sexual functions and appetite and its effects on the offspring of the users of the drug. *Tr M Soc Tennessee*. 1892;162–179
6. Earle FB. Maternal opium habit and infant mortality. *M Standard (Chicago)*. 1888;3:2
7. OD. Fetal morphine addiction, queries and minor notes. *JAMA*. 1903;40:1092
8. Perlstein MA. Congenital morphinism; a rare cause of convulsions in the newborn. *J Am Med Assoc*. 1947;135(10):633
9. Goodfriend MJ, Shey IA, Klein MD. The effects of maternal narcotic addiction on the newborn. *Am J Obstet Gynecol*. 1956;71(1):29–36
10. Cobrinik RW, Hood RT Jr, Chusid E. The effect of maternal narcotic addiction on the newborn infant; review of literature

and report of 22 cases. *Pediatrics*. 1959; 24(2):288–304

11. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA*. 1998;280(22):1936–1943
12. Reddy AM, Harper RG, Stern G. Observations on heroin and methadone withdrawal in the newborn. *Pediatrics*. 1971; 48(3):353–358
13. Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, Tignol J. French field experience with buprenorphine. *Am J Addict*. 2004;13(suppl 1):S17–S28
14. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) series 40. Rockville, MD: Substance Abuse and Mental Health Administration; 2004. DHHS publication (SMA) 04-3939
15. Marquet P, Chevrel J, Lavignasse P, Merle L, Lachâtre G. Buprenorphine withdrawal syndrome in a newborn. *Clin Pharmacol Ther*. 1997;62(5):569–571
16. Kayemba-Kay's S, Laclyde JP. Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. *Addiction*. 2003;98(11): 1599–1604
17. Rao R, Desai NS. OxyContin and neonatal abstinence syndrome. *J Perinatol*. 2002;22 (4):324–325
18. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA*. 2012;307(18): 1934–1940
19. O'Donnell M, Nassar N, Leonard H, et al. Increasing prevalence of neonatal withdrawal syndrome: population study of maternal factors and child protection involvement. *Pediatrics*. 2009;123(4). Available at: www.pediatrics.org/cgi/content/full/123/4/e614
20. SAMHSA. Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2008-2011. Available at: www.samhsa.gov/data/NSDUH/2011SummNatFindDetTables/NSDUH-DetTabsPDFWHTML2011/2k11DetailedTabs/Web/HTML/NSDUH-DetTabsSect6peTabs55to107-2011.htm#Tab6.72A. Accessed February 25, 2013
21. Napolitano A, Theophilopoulos D, Seng SK, Calhoun DA. Pharmacologic management of neonatal abstinence syndrome in a community hospital. *Clin Obstet Gynecol*. 2013;56(1):193–201
22. Patrick SW, Benneyworth BD, Schumacher R, Davis MM. Variation in hospital type in treatment of neonatal abstinence syndrome in the United States. Paper presented at Pediatric Academic Societies Annual Meeting; May 4–7, 2013; Washington, DC. Abstract 2922
23. Tetstall E, Liu AJ, An EI, Canalese J, Nanan R. Pregnancy and neonatal characteristics of opioid-dependent Indigenous Australians: a rural and metropolitan comparison. *Aust N Z J Obstet Gynaecol*. 2009;49(3): 279–284
24. Substance Abuse and Mental Health Administration. Report TEDS. Injection drug abuse admission to substance abuse treatment, 1999 to 2009. Available at: www.samhsa.gov/data/2k11/WEB_TEDS_012/WEB_TEDS_012.htm. Accessed February 25, 2013
25. Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use: the international experience. *Clin Infect Dis*. 2006;43(suppl 4):S197–S215
26. Shainker SA, Saia K, Lee-Parritz A. Opioid addiction in pregnancy. *Obstet Gynecol Surv*. 2012;67(12):817–825
27. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CJ, eds. Teratology and medications that affect the fetus. In: *Williams Obstetrics*. 23rd ed. New York, NY: McGraw Hill; 2010:328
28. Kandall SR, Doberczak TM, Jantunen M, Stein J. The methadone-maintained pregnancy. *Clin Perinatol*. 1999;26(1):173–183
29. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Effects and management. *Obstet Gynecol Clin North Am*. 1998;25(1):139–151
30. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharmacol Exp Ther*. 1985; 233(1):1–6
31. Jarvis MA, Wu-Pong S, Kniseley JS, Schnoll SH. Alterations in methadone metabolism during late pregnancy. *J Addict Dis*. 1999; 18(4):51–61
32. Seligman NS, Almario CV, Hayes EJ, Dysart KC, Berghella V, Baxter JK. Relationship between maternal methadone dose at delivery and neonatal abstinence syndrome. *J Pediatr*. 2010;157(3):428–433, e1
33. Lim S, Prasad MR, Samuels P, Gardner DK, Cordero L. High-dose methadone in pregnant women and its effect on neonatal abstinence syndrome. *Am J Obstet Gynecol*. 2009;200:70.e1–70.e5
34. Pizarro D, Habli M, Grier M, Bombrys A, Sibai B, Livingston J. Higher maternal doses of methadone does not increase neonatal abstinence syndrome. *J Subst Abuse Treat*. 2011;40(3):295–298
35. Dashe J, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. *Obstet Gynecol*. 2002;100:1244–1258
36. McCarthy JJ, Leamon MH, Parr MS, Anania B. High-dose methadone maintenance in pregnancy: maternal and neonatal outcomes. *Am J Obstet Gynecol*. 2005;193(3 pt 1):606–610
37. Cleary BJ, Donnelly J, Strawbridge J, et al. Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis. *Addiction*. 2010;105(12):2071–2084
38. Riksheim M, Gossop M, Clausen T. From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme. *J Subst Abuse Treat*. 2014;46:291–294
39. Soyka M. Buprenorphine use in pregnant opioid users: a critical review. *CNS Drugs*. 2013;27(8):653–662
40. Jones HE, Heil SH, Baewert A, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. *Addiction*. 2012;107(suppl 1):5–27
41. Jones HE, Johnson RE, Jasinski DR, et al. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*. 2005;79(1):1–10
42. Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S; Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. *Drug Alcohol Depend*. 2006; 82(3):250–257
43. Fischer G, Ortner R, Rohrmeister K, et al. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction*. 2006;101(2):275–281
44. Kakko J, Heilig M, Sarman I. Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend*. 2008;96(1-2):69–78
45. Bakstad B, Sarfi M, Welle-strand G, Ravndal E. Opioid maintenance treatment during pregnancy: occurrence and severity of neonatal abstinence syndrome. A national prospective study. *Eur Addict Res*. 2009;15 (3):128–134
46. Lacroix I, Berrebi A, Garipuy D, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective

multicenter study. *Eur J Clin Pharmacol*. 2011;67:1053–1059

47. Welle-Strand GK, Skurtveit S, Jones HE, et al. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. *Drug Alcohol Depend*. 2013;127(1-3):200–206
48. Patel P, Abdel-Latif ME, Hazelton B, et al. Perinatal outcomes of Australian buprenorphine-exposed mothers and their newborn infants. *J Paediatr Child Health*. 2013;49(9):746–753
49. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320–2331
50. Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013;(12): CD006318
51. Jones HE, Dengler E, Garrison A, et al. Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy. *Drug Alcohol Depend*. 2014; 134:414–417
52. Epstein RA, Bobo WV, Martin PR, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Ann Epidemiol*. 2013;23(8):498–503
53. Buchi KF, Suarez C, Varner MW. The prevalence of prenatal opioid and other drug use in Utah. *Am J Perinatol*. 2013;30(3): 241–244
54. Handal M, Engeland A, Rønning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *Eur J Clin Pharmacol*. 2011;67 (9):953–960
55. Committee on Health Care for Underserved Women, The American College of Obstetricians and Gynecologists. Committee opinion no. 538: nonmedical use of prescription drugs. *Obstet Gynecol*. 2012; 120(4):977–982
56. Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. *Am J Obstet Gynecol*. 2011;204:259.e1–e4
57. Kelly L, Dooley J, Cromarty H, et al. Narcotic-exposed neonates in a First Nations population in northwestern Ontario: incidence and implications. *Can Fam Physician*. 2011;57(11):e441–e447
58. Winchester PD, Miller K, Proctor C, Singhal A, Ying J, Ellis G. Neonatal abstinence and opiate prescriptions. Paper presented at Pediatric Academic Societies Annual Meeting; April 28–May 1, 2012; Boston, MA. Abstract
59. Brown MS, Hayes MJ, LaBrie S. Breastfeeding is associated with decreased risk and length of treatment for neonatal abstinence syndrome in methadone and buprenorphine exposed infants. Paper presented at Pediatric Academic Societies; May 1–4, 2011; Vancouver, BC, Canada. Abstract
60. Kocherlakota P. Changing spectrum of neonatal abstinence syndrome. Paper presented at Pediatric Academic Societies; April 28–May 1, 2012; Boston, MA. Abstract
61. ACOG Committee on Practice Bulletins; Obstetrics. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008;111(4):1001–1020
62. Fenger-Gron J, Thomsen M, Andersen KS, Nielsen G. Pediatric outcomes following intrauterine exposure to serotonin reuptake inhibitors: a systemic review. *Dan Med Bul*. 2011;58:A4303
63. Stephansson O, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of stillbirth and infant mortality. *JAMA*. 2013;309(1): 48–54
64. Kieviet N, Dolman KM, Honig A. The use of psychotropic medication during pregnancy: how about the newborn? *Neuropsychiatr Dis Treat*. 2013;9:1257–1266
65. Substance Abuse and Mental Health Services Administration. Center for Behavioral Health Statistics and Quality. Results from the 2012 National Survey on Drug Use and Health: summary of national findings. Available at: www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.pdf. Accessed January 14, 2014
66. United Nations Office on Drugs and Crime. Global smart update 2012. Volume 8. Available at: www.unodc.org/documents/scientific/Global_SMART_Update_8_E_web.pdf. Accessed January 24, 2014
67. Oei JL, Kingsbury A, Dhawan A, et al. Amphetamines, the pregnant woman and her children: a review. *J Perinatol*. 2012;32 (10):737–747
68. Jones HE, Balster RL. Inhalant abuse in pregnancy. *Obstet Gynecol Clin North Am*. 1998;25(1):153–167
69. Behnke M, Smith VC; Committee on Substance Abuse and Committee on Fetus and Newborn. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics*. 2013;131(3). Available at: www.pediatrics.org/cgi/content/full/131/3/e1009
70. Tenenbein M, Casiro OG, Seshia MM, Debooy VD. Neonatal withdrawal from maternal volatile substance abuse. *Arch Dis Child Fetal Neonatal Ed*. 1996;74(3):F204–F207
71. Nanovskaya TN, Nekhayeva, Hankins GDV, Ahmed MS. Transfer of methadone across the dually perfused preterm human placental lobule. *Am J Obstet Gynecol*. 2008: 198:126.e1–e4
72. Szeto HH. Kinetics of drug transfer to the fetus. *Clin Obstet Gynecol*. 1993;36(2):246–254
73. Malek A, Obrist C, Wenzinger S, von Mandach U. The impact of cocaine and heroin on the placental transfer of methadone. *Reprod Biol Endocrinol*. 2009;7:61
74. Scott CS, Riggs KW, Ling EW, et al. Morphine pharmacokinetics and pain assessment in premature newborns. *J Pediatr*. 1999;135 (4):423–429
75. Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y. Current research on opioid receptor function. *Curr Drug Targets*. 2012;13(2): 230–246
76. Barr GA, McPhie-Lalmansingh A, Perez J, Riley M. Changing mechanisms of opiate tolerance and withdrawal during early development: animal models of the human experience. *ILAR J*. 2011;52:329–341
77. Rehni AK, Jaggi AS, Singh N. Opioid withdrawal syndrome: emerging concepts and novel therapeutic targets. *CNS Neurol Disord Drug Targets*. 2013;12(1):112–125
78. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*. 2013;248:637–654
79. Little PJ, Price RR, Hinton RK, Kuhn CM. Role of noradrenergic hyperactivity in neonatal opiate abstinence. *Drug Alcohol Depend*. 1996;41(1):47–54
80. Spiga S, Puddu MC, Pisano M, Diana M. Morphine withdrawal-induced morphological changes in the nucleus accumbens. *Eur J Neurosci*. 2005;22(9):2332–2340
81. Radke AK, Rothwell PE, Gewirtz JC. An anatomical basis for opponent process mechanisms of opiate withdrawal. *J Neurosci*. 2011;31(20):7533–7539
82. Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. *Trends Neurosci*. 2013;36(3):195–206
83. Lauden J, Kerby LG. Opiate exposure and withdrawal dynamically regulate mRNA expression in the serotonergic dorsal raphe nucleus. *Neuroscience*. 2013;254: 160–172

84. Capasso A, Gallo C. Molecules acting on CB1 receptor and their effects on morphine withdrawal in vitro. *Open Biochem J*. 2009;3:78–84
85. Nunez C, Földes A, Laorden ML, Milanes MV, Kovács KJ. Activation of stress-related hypothalamic neuropeptide gene expression during morphine withdrawal. *J Neurochem*. 2007;101(4):1060–1071
86. Pasero C, McCaffery M. Opioid-induced hyperalgesia. *J Perianesth Nurs*. 2012;27 (1):46–50
87. Juul SE, Beyer RP, Bammler TK, Farin FM, Gleason CA. Effects of neonatal stress and morphine on murine hippocampal gene expression. *Pediatr Res*. 2011;69(4):285–292
88. Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. *J Pediatr*. 1991;118 (6):933–937
89. Anand KJS, Anderson BJ, Holford NHG, et al; NEOPAIN Trial Investigators Group. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth*. 2008;101(5):680–689
90. Dysart K, Hsieh HC, Kaltenbach K, Greenspan JS. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: differential course of neonatal abstinence syndrome. *J Perinat Med*. 2007;35(4):344–346
91. Sanj EJ, De-las-Cuevas C, Kiuru A, Bate A, Edwards R. Selective serotonin inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet*. 2005;365(9458):482–487
92. Chiu VM, Schenk JO. Mechanism of action of methamphetamine within the catecholamine and serotonin areas of the central nervous system. *Curr Drug Abuse Rev*. 2012;5(3):227–242
93. Gaalema DE, Scott TL, Heil SH, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates. *Addiction*. 2012;107(suppl 1):53–62
94. Herzlinger RA, Kandall SR, Vaughan HG Jr. Neonatal seizures associated with narcotic withdrawal. *J Pediatr*. 1977;91(4): 638–641
95. Jansson LM, Dipietro JA, Elko A, Velez M. Infant autonomic functioning and neonatal abstinence syndrome. *Drug Alcohol Depend*. 2010;109(1-3):198–204
96. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and NewbornAmerican Academy of Pediatrics Clinical Report. Neonatal drug withdrawal. *Pediatrics*. 2012; 129(2). Available at: www.pediatrics.org/cgi/content/full/129/2/e540
97. Seligman NS, Salva N, Hayes EJ, Dysart KC, Pequignot EC, Baxter JK. Predicting length of treatment for neonatal abstinence syndrome in methadone exposed neonates. *Am J Obstet Gynecol*. 2008;199:396.e1–396.e7
98. Liu AJW, Jones MP, Murray H, Cook CM, Nanan R. Perinatal risk factors for the neonatal abstinence syndrome in infants born to women on methadone maintenance therapy. *Aust N Z J Obstet Gynaecol*. 2010;50(3):253–258
99. Dryden C, Young D, Hepburn M, Mactier H. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. 2009;116(5):665–671
100. Sie SD, Wennink JM, van Driel JJ, et al. Maternal use of SSRIs, SNRIs and NaSSAs: practical recommendations during pregnancy and lactation. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F472–F476
101. Chomchai C, Manaboriboon B. Stimulant methamphetamine and dextromethorphan use among Thai adolescents: implications for health of women and children. *J Med Toxicol*. 2012;8(3):291–294
102. Gaalema DE, Heil SH, Badger GJ, Metayer JS, Johnston AM. Time to initiation of treatment for neonatal abstinence syndrome in neonates exposed in utero to buprenorphine or methadone. *Drug Alcohol Depend*. 2013;133(1):266–269
103. Oei J, Lui K. Management of the newborn infant affected by maternal opiates and other drugs of dependency. *J Paediatr Child Health*. 2007;43(1–2):9–18
104. Cleary BJ, Eogan M, O'Connell MP, et al. Methadone and perinatal outcomes: a prospective cohort study. *Addiction*. 2012;107(8):1482–1492
105. Wachman EM, Hayes MJ, Brown MS, et al. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *JAMA*. 2013;309(17): 1821–1827
106. Jansson LM, Di Pietro JA, Elko A, Williams EL, Milio L, Velez M. Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: a comparison of fetal neurobehaviors and infant outcomes. *Drug Alcohol Depend*. 2012;122(3):213–219
107. Johnson K, Greenough A, Gerada C. Maternal drug use and length of neonatal unit stay. *Addiction*. 2003;98(6):785–789
108. Dabek MT, Porschl J, Englert S, Ruef P. Treatment of neonatal abstinence syndrome in preterm and term neonates. *Klin Padiatr*. 2013;225(5):252–256
109. Kaltenbach K, Holbrook AM, Coyle MG, et al. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. *Addiction*. 2012;107(suppl 1): 45–52
110. Irner TB, Teasdale TW, Nielsen T, Vedal S, Olofsson M. Substance use during pregnancy and postnatal outcomes. *J Addict Dis*. 2012;31(1):19–28
111. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstet Gynecol Neonatal Nurs*. 2102;41: 180–190
112. O'Connor AB, O'Brien L, Alto WA. Are there gender related differences in neonatal abstinence syndrome following exposure to buprenorphine during pregnancy? *J Perinat Med*. 2013;41(5):621–623
113. Unger A, Jagsch R, Bäwert A, et al. Are male neonates more vulnerable to neonatal abstinence syndrome than female neonates? *Gend Med*. 2011;8(6):355–364
114. Jones HE, Heil SH, Tuten M, et al. Cigarette smoking in opioid-dependent pregnant women: neonatal and maternal outcomes. *Drug Alcohol Depend*. 2013;131(3):271–277
115. Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med*. 2011;5 (4):293–299
116. Cotten SW. Drug testing in the neonate. *Clin Lab Med*. 2012;32(3):449–466
117. Ostrea EM Jr, Knapp DK, Tannenbaum L, et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. *J Pediatr*. 2001;138(3):344–348
118. Lozano J, García-Algar O, Vall O, de la Torre R, Scaravelli G, Pichini S. Biological matrices for the evaluation of in utero exposure to drugs of abuse. *Ther Drug Monit*. 2007;29(6):711–734
119. Gourlay DL, Heit HA, Caplan YH. Urine drug testing in clinical practice: the art and science of patient care. 5th ed. Baltimore, MD: Johns Hopkins University School of Medicine; 2012
120. Cotten SW, Duncan DL, Burch EA, Seashore CJ, Hammett-Stabler CA. Unexpected interference of baby wash products with a cannabinoid (THC) immunoassay. *Clin Biochem*. 2012;45(9):605–609
121. Wu AH, Gerona R, Armenian P, French D, Petrie M, Lynch KL. Role of liquid chromatography-high-resolution mass spectrometry (LC-HR/MS) in clinical toxicology. *Clin Toxicol (Phila)*. 2012;50(8):733–742

122. Kerrigan S, Mott A, Jatzlau B, et al. Designer psychostimulants in urine by liquid chromatography-tandem mass spectrometry. *J Forensic Sci*. 2014;59(1):175–183
123. Ingall GB. Alcohol biomarkers. *Clin Lab Med*. 2012;32(3):391–406
124. Murphy-Oikonen J, Montelpare WJ, Southon S, Bertoldo L, Persichino N. Identifying infants at risk for neonatal abstinence syndrome: a retrospective cohort comparison study of 3 screening approaches. *J Perinat Neonatal Nurs*. 2010;24(4):366–372
125. Hytinantti T, Kahila H, Renlund M, Järvenpää AL, Halmesmäki E, Kivitie-Kallio S. Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero. *Acta Paediatr*. 2008;97(8):1040–1044
126. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1–2):141–158
127. Mehta A, Forbes KD, Kuppala VS. Neonatal abstinence syndrome management from prenatal counseling to a post discharge follow-up care: results of a national survey. *Hosp Pediatr*. 2013;3(4):317–323
128. Maguire D, Cline GJ, Parnell L, Tai CY. Validation of the Finnegan Neonatal Abstinence Syndrome Tool-short form. *Adv Neonatal Care*. 2013;13(6):430–437
129. Zahorodny W, Rom C, Whitney W, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *J Dev Behav Pediatr*. 1998;19(2):89–93
130. Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. *J Perinatol*. 2006;26(1):15–17
131. van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpen TW, L'Hoir MP. Swaddling: a systematic review. *Pediatrics*. 2007;120(4). Available at: www.pediatrics.org/cgi/content/full/120/4/e1097
132. Caiola E. Swaddling young infants can decrease crying time. *J Pediatr*. 2007;150(3):320–321
133. D'Apolito K. Comparison of a rocking bed and standard bed for decreasing withdrawal symptoms in drug-exposed infants. *MCN Am J Matern Child Nurs*. 1999;24(3):138–144
134. American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. *Pediatrics*. 1998;101(6):1079–1088
135. Filippelli AC, White LF, Spellman LW, et al. Non-insertive acupuncture and neonatal abstinence syndrome: a case series from an inner city safety net hospital. *Glob Adv Health Med*. 2012;1(4):48–52
136. Hunseler C, Bruckle M, Roth B, Kribs A. Neonatal opiate withdrawal and rooming in: a retrospective analysis of a single center experience. *Klin Padiatr*. 2013;225(5):247–251
137. Hodgson ZG, Abrahams RR. A rooming-in program to mitigate the need to treat for opiate withdrawal in the newborn. *J Obstet Gynaecol Can*. 2012;34(5):475–481
138. Kuschel C. Managing drug withdrawal in the newborn infant. *Semin Fetal Neonatal Med*. 2007;12(2):127–133
139. Greig E, Ash A, Douiri A. Maternal and neonatal outcomes following methadone substitution during pregnancy. *Arch Gynecol Obstet*. 2012;286(4):843–851
140. Finnegan L, Kaltenach K. Neonatal abstinence syndrome. In: Hoekalman R, Friedman S, Nelson N, Sidel H, eds. Primary Pediatric Care. St Louis, MO: Mosby-Year Book; 1992: 1367–1378
141. Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. *Pediatr Clin North Am*. 2012;59(5):1147–1165
142. Sublett J. Neonatal abstinence syndrome: therapeutic interventions. *MCN Am J Matern Child Nurs*. 2013;38(2):102–107, quiz 107–109
143. Grim K, Harrison TE, Wilder RT. Management of neonatal abstinence syndrome from opioids. *Clin Perinatol*. 2013;40(3):509–524
144. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. *Cochrane Database Syst Rev*. 2010;(10):CD002053
145. O'Grady MJ, Hopewell J, White MJ. Management of neonatal abstinence syndrome: a national survey and review of practice. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(4):F249–F252
146. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag*. 2009;5(1):47–55
147. Backes CH, Backes CR, Gardner D, Nankervis CA, Giannone PJ, Cordero L. Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting. *J Perinatol*. 2012;32(6):425–430
148. Sauberan J, Rossi S, Kim JH. Stability of dilute oral morphine solution for neonatal abstinence syndrome. *J Addict Med*. 2013;7(2):113–115
149. Jackson L, Ting A, McKay S, Galea P, Skeoch C. A randomised controlled trial of morphine versus phenobarbitone for neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2004;89(4):F300–F304
150. Bio LL, Siu A, Poon CY. Update on the pharmacologic management of neonatal abstinence syndrome. *J Perinatol*. 2011;31(11):692–701
151. Kapur BM, Hutson JR, Chibber T, Luk A, Selby P. Methadone: a review of drug-drug and pathophysiological interactions. *Crit Rev Clin Lab Sci*. 2011;48(4):171–195
152. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. *Addiction*. 2011;106(3):574–580
153. Leikin JB, Mackendrick WP, Maloney GE, et al. Use of clonidine in the prevention and management of neonatal abstinence syndrome. *Clin Toxicol (Phila)*. 2009;47(6):551–555
154. Esmaeili A, Keinhorst AK, Scuster T, Beske F, Schosser R, Basanier C. Treatment of neonatal abstinence syndrome with clonidine and chloral hydrate. *Acta Paediatr*. 2010;99(2):209–214
155. Agthe AG, Kim GR, Mathias KB, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. 2009;123(5). Available at: www.pediatrics.org/cgi/content/full/123/5/e849
156. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776–789
157. Sachs HC. Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132(3): Available at www.pediatrics.org/cgi/content/full/132/3/e796
158. Jansson LM, Choo R, Velez ML, et al. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics*. 2008;121(1):106–114
159. McCarthy JJ, Posey BL. Methadone levels in human milk. *J Hum Lact*. 2000;16(2):115–120
160. Ilett KF, Hackett LP, Gower S, Doherty DA, Hamilton D, Bartu AE. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. *Breastfeed Med*. 2012;7:269–274
161. ACOG Committee on Health Care for Underserved Women; American Society of Addiction Medicine. ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. *Obstet Gynecol*. 2012;119(5):1070–1076
162. Jansson LM; Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #21: Guidelines for breastfeeding

and the drug-dependent woman. *Breastfeed Med.* 2009;4(4):225–228

163. O'Connor AB, Collett A, Alto WA, O'Brien LM. Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy. *J Midwifery Womens Health.* 2013;58(4):383–388
164. Bogen DL, Perel JM, Helsel JC, Hanusa BH, Thompson M, Wisner KL. Estimated infant exposure to enantiomer-specific methadone levels in breastmilk. *Breastfeed Med.* 2011;6(6):377–384
165. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. *J Hum Lact.* 2009;25(2):199–205
166. Isemann B, Meinzen-Derr J, Akinbi H. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. *J Perinatol.* 2011;31(1):25–29
167. Sauberan JB, Anderson PO, Lane JR, et al. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. *Obstet Gynecol.* 2011;117(3):611–617
168. Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol.* 2007;47(3):181–185
169. Madadi P, Avard D, Koren G. Pharmacogenetics of opioids for the treatment of acute maternal pain during pregnancy and lactation. *Curr Drug Metab.* 2012;13(6):721–727
170. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *Acta Paediatr.* 2013;102(11):1060–1066
171. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. *Pediatrics.* 2006;117(6). Available at: www.pediatrics.org/cgi/content/full/117/6/e1163
172. Wachman EM, Byrun J, Philip BL. Breast feeding rates among mothers of infants with neonatal abstinence syndrome. Paper presented at Pediatric Academic Society Meeting; May 1–4, 2012; Boston, MA
173. Conradt E, Sheinkopf SJ, Lester BM, et al. Prenatal substance exposure: neurobiological organization at 1 month. *J Pediatr.* 2013;163(4):989–994.ei
174. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Hum Dev.* 2008;84(1):29–35
175. Lester BM, Lagasse LL. Children of addicted women. *J Addict Dis.* 2010;29(2):259–276
176. Mei B, Niu L, Cao B, Huang D, Zhou Y. Prenatal morphine exposure alters the layer II/III pyramidal neurons morphology in lateral secondary visual cortex of juvenile rats. *Synapse.* 2009;63(12):1154–1161
177. Massa H, Lacoh CM, Vutskits L. Effects of morphine on the differentiation and survival of developing pyramidal neurons during the brain growth spurt. *Toxicol Sci.* 2012;130(1):168–179
178. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. *Pediatr Neurol.* 2012;47(1):1–6
179. Walhovd KB, Moe V, Slinning K, et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. *Neuroimage.* 2007;36(4):1331–1344
180. Gentile S. Neurodevelopmental effects of prenatal exposure to psychotropic medications. *Depress Anxiety.* 2010;27(7):675–686
181. Hviid A, Melbye M, Pasternak B. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. *N Engl J Med.* 2013;369(25):2406–2415
182. Smith LM, LaGasse LL, Derauf C, et al. Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. *Neurotoxicol Teratol.* 2011;33(1):176–184
183. Visconti K, Hennessy K, Towers C, Hannessy M, Howard B. Opiate abuse/usage in pregnancy and newborn head circumference. *Am J Obstet Gynecol.* 2013;208:S67–S68
184. Sundelin Wahlsten V, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr.* 2013;102(5):544–549
185. Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K. Strabismus in infants of opiate-dependent mothers. *Acta Paediatr.* 2003;92(3):379–385
186. Spiteri Cornish K, Hrabovsky M, Scott NW, Myerscough E, Reddy AR. The short- and long-term effects on the visual system of children following exposure to maternal substance misuse in pregnancy. *Am J Ophthalmol.* 2013;156(1):190–194
187. McGlone L, Hamilton R, McCulloch DL, et al. Neonatal visual evoked potentials in infants born to mothers prescribed methadone. *Pediatrics.* 2013;131(3). Available at: www.pediatrics.org/cgi/content/full/131/3/e857

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