



Identifying and Assessing the Substance-Exposed Infant

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Abstract

As the rate of opioid prescription grows, so does fetal exposure to opioids during pregnancy. With increasing fetal exposure to both prescription and nonprescription drugs, there has been a concurrent increase in identification of Neonatal Withdrawal Syndrome (NWS) and adaptation difficulties after birth. In addition, extended use of opioids, barbiturates, and benzodiazepines in neonatal intensive care has resulted in iatrogenic withdrawal syndromes. There is a lack of evidence to support the use of any one specific evaluation strategy to identify NWS. Clinicians caring for infants must use a multimethod approach to diagnosis, including interview and toxicology screening. Signs of NWS are widely variable, and reflect dysfunction in autonomic regulation, state control, and sensory and motor functioning. Several assessment tools have been developed for assessing severity of withdrawal in term neonates. These tools assist in determining need and duration of pharmacologic therapy and help in titration of these therapies. Considerable variability exists in the pharmacologic and nonpharmacologic approaches to affected babies across settings. An evidence-based protocol for identification, evaluation, and management of NWS should be in place in every nursery. This article provides an overview of identification and assessment considerations for providers who care for babies at risk for or who are experiencing alterations in state, behavior, and responses after prenatal or iatrogenic exposure to agents associated with the spectrum of withdrawal.

Key words: Drug addiction; Infant; Neonatal; Neonatal Abstinence Syndrome; Serotonin Syndrome; Substance withdrawal.

Neonatal Withdrawal Syndrome (NWS) is a term introduced over 2 decades ago to describe the variable spectrum of signs of neonatal neurologic and behavioral dysregulation that occur as a result of withdrawal from certain psychoactive drugs, particularly those that cause addiction in adults (Levy & Spino, 1993). Neurobehavioral findings associated specifically with opioid withdrawal at birth, following in-utero exposure, have been termed Neonatal Abstinence Syndrome (NAS) (Hudak & Tan, 2012).

As the rate of opiate prescription grows, so does fetal exposure to opioids in pregnancy (Substance Abuse and Mental Health Services Administration, 2011). Neonates who are treated with opiates, as well as barbiturates and benzodiazepines, are at risk for exhibiting signs of NWS. Appropriate management of neonates at risk for withdrawal, or who develop NWS, requires complex, recurrent neurobehavioral assessment. Such assessment is commonly accomplished by neonatal and pediatric nurses.

Incidence, Prevalence, and Cost to Society

Results of the 2010 National Survey of Drug Use and Health, an annual survey sponsored by the Substance Abuse and Mental Health Services Administration, found approximately 22.6 million, or 8.9% of Americans, aged 12 years and older, were current or past month illicit drug users (Substance Abuse and Mental Health Services Administration, 2011). Over 238 million prescriptions were written for opioid analgesics in 2011 (Substance Abuse and Mental Health Services Administration, 2011). The impact of this trend on pregnant women, and the transfer of opioid addiction to their babies, present major challenges to clinicians responsible for identifying and treating NWS.

Drug use in pregnancy has been difficult to quantify; however, there appears to be an increasing prevalence of chronic narcotic among pregnant women (Kellogg, Rose, Harms, & Watson, 2011). Between 2000 and 2009, it was estimated that prenatal maternal opiate use increased from 1.2 to 5.6 per 1,000 live hospital births per year (Patrick et al., 2012). In the United States, methadone and heroin are the most common opioids implicated in prenatal exposure, although incidence of fetal exposure to hydrocodone and buprenorphine is increasing (Manchikanti, Fellows, Ailani, & Pampati, 2010).

Between 2000 and 2009, the incidence of NWS among newborns

increased from 1.2 to 3.4 per 1,000 hospital births per year, with iatrogenic NWS accounting for only 5% of all cases (Patrick et al., 2012). Iatrogenic NWS is related to extended use of opioids, barbiturates, and/or benzodiazepines in the newborn period. The increasing incidence of NWS is associated with growing costs. In 2009, it was estimated that the mean charge for a hospitalization associated with NWS was \$53,400. Between 2000 and 2009, total hospital charges for NWS in the United States increased from \$190 million to \$720 million. In 2009, over 13,500 newborns were treated for NWS in the United States, representing approximately one baby per hour (Patrick et al., 2012).

Consensus Statements

In 2012, the American Academy of Pediatrics' (AAP) Committee on Drugs released recommendations for identifying, assessing, and managing substance-exposed neonates (Hudak & Tan, 2012). The AAP Committee on Drugs has recommended the following approach for detection:

- Hospitals should adopt policies for maternal and newborn screening that avoid discriminatory practices and comply with local laws.
- Signs of withdrawal may mimic other conditions; therefore, alternate diagnoses (e.g., infection, electrolyte imbalance, intracranial hemorrhage, hypoxic-ischemic encephalopathy) should also be explored when NWS is being considered.
- When NWS is suspected, a detailed drug history should be obtained by interviewing the mother, and include inquiry into prescription and nonprescription drug use, as well as use by partners, friends, and parents.
- Maternal interviewing is recognized to underestimate fetal substance exposure; thus, biological screening (e.g., urine, meconium, cord tissue) should be done in suspect cases.

The AAP Committee on Drugs (Hudak & Tan, 2012) also recommended approaches for ongoing assessment and management of neonates with NWS or at risk for withdrawal, including all nurseries should adopt a protocol for the evaluation and management of neonatal withdrawal, and all clinicians should be provided education on use of a published abstinence assessment tool. Maternity unit- and nursery-specific protocols should reflect current state of the science. When developing or implementing guidelines for detection and management of NWS, it is important to recognize limitations of current screening, assessment, and treatment methods.

Risk Factors for Developing NWS

Fetal opioid exposure is increasingly common; however, clinically significant NWS likely occurs in only a relatively small percentage of exposed babies. Early researchers reported rates of withdrawal from prenatal opioids of 55% to 94% (Fricker & Segal, 1978; Harper, Solish, Feingold, Gersten-Woelf, & Sokal, 1977; Madden et al., 1977). Researchers acknowledged, however, difficulties in determining actual prenatal opioid usage rates. More recently, in a prospective study examining a large cohort of opioid-maintained women over a 10-year period, it was found that NWS occurred in 5.6% of neonates whose mothers used prescription narcotics in pregnancy (Kellogg et al., 2011).

Both methadone and buprenorphine (either alone or in combination with naloxone) have been used to treat opioid addiction in pregnant women despite their categorizations as class C pregnancy drugs (Jones et al., 2014). These drugs are recognized as the standard of care for treating opioid addiction in pregnancy and seem to be associated with a higher incidence of clinically significant NWS when compared to illicitly used opioids (Binder &

Vavrinková, 2008). Development of NWS following methadone and buprenorphine exposure appears to be variable and not necessarily associated with dosage (Bakstad, Sarfi, Welle-Strand, & Ravndal, 2009). In a retrospective study of 100 mother-infant pairs, researchers found no correlation between maternal methadone dosage and incidence of NWS (Berghella et al., 2003). Buprenorphine may have an advantage to methadone in treating maternal addiction due to shorter treatment duration for NWS (Jones et al., 2010).

Timing of NWS symptoms can be anticipated based on the half-life of drugs to which the fetus was prenatally exposed. Babies can experience withdrawal symptoms within 6 hours of birth for short-acting opioids (such as heroin), whereas long-acting opiates (such as methadone) typically produce withdrawal symptoms after 36 hours (Lugo, Satterfield, & Kern, 2005).

Gestational age appears to affect severity of NWS, with milder signs developing in more premature infants. The reason for this blunted presentation may be central nervous system (CNS) immaturity or lower fat deposits in the premature infant, or decreased total drug exposure (Jansson, Dipietro, Elko, & Velez, 2010; Logan, Brown, & Hayes, 2013). The severity of iatrogenic NWS has been thought to more closely approximate dose and duration of hospital therapy. Opioid therapy exceeding 5 to 7 days has been consistently implicated as a risk factor for NWS (Cramton & Gruchala, 2013).

There has been increasing interest in the association between maternal antidepressants and withdrawal signs in the newborn. Selective serotonin reuptake inhibitors (SSRIs) are frequently used to treat depression in pregnant women. Third trimester exposure to SSRI antidepressants has been associated with a constellation of neonatal signs that are similar to those observed in NWS (Jansson & Velez, 2012). Although SSRI antidepressants have

the potential to cause NWS, it has been suggested that some of these cases may in fact represent serotonin toxicity, or a combination of withdrawal and toxicity. It can be difficult to distinguish between withdrawal and toxicity, because signs are nonspecific and similar, although plasma concentrations of psychotropic drugs are generally low in withdrawal and high in toxicity (Alwan & Friedman, 2009). The terms Serotonin Syndrome, Postnatal Adaptation Syndrome, and Prenatal Antidepressant Exposure Syndrome have been used to describe these phenomena (Gentile, 2010; Haddad, Pal, Clarke, Wieck, & Sridhiran, 2005; Kieviet, Dolman, & Honig,

2013). A compilation of drugs that have been associated with signs of withdrawal/toxicity in neonates, or that have properties implicated in NWS, are listed in Table 1.

Identification and Assessment of NWS

As suggested by the AAP guidelines, there remains a lack of evidence to support the use of any one specific evaluation strategy to identify NWS (Hudak & Tan, 2012). Therefore, clinicians must adapt a multimethod approach. Maternal interview targeting prenatal substance exposure is commonly used; however, this approach has flaws. Maternal fear, guilt,

and shame related to drug use limit truthful discussions between women and their healthcare providers (Murphy-Oikonen, Montelpare, Southon, Bertoldo, & Persichino, 2010).

Selective newborn toxicology screening using biological samples is another identification method, but also limited by testing sensitivity, timing requirements, and the application of screening criteria (Murphy-Oikonen et al., 2010). Drug addiction in the United States has changed over the past few years. Illicit use of prescription psychotherapeutics and opioids now overshadows the use of nonprescription illicit drugs (Manchikanti et al., 2010). Selective screening criteria should be regularly

Table 1: Substances Associated with Signs of Neonatal Withdrawal/Toxicity (or with Properties Associated with Neonatal Withdrawal Syndrome)

Opioids/Narcotics	CNS Stimulants	CNS Depressants	Hallucinogens	Other Psychotropics
Buprenorphine Codeine Fentanyl Heroin Hydrocodone Hydromorphone Levorphanol Meperidine Methadone Morphine Naloxone Naltrexone Opium Oxycodone Oxymorphone Pentazocine Propoxyphene Tapentadol Tramadol	Amphetamine Caffeine Cocaine Dexamphetamine Dextroamphetamine Fenfluramine Gamma-Hydroxybutyric acid Methamphetamine Methylphenidate Nicotine Pemoline Phencyclidines Phendimetrazine Phentermine Phenylpropanolamine Pseudoephedrine	Alcohol Barbiturates Amobarbital Butabarbital Butalbital Methohexital Pentobarbital Phenobarbital Secobarbital Thiopental Benzodiazepines Alprazolam Chlordiazepoxide Clonazepam Diazepam Flurazepam Lorazepam Midazolam Oxazepam Temazepam Triazolam Cannabinoids Chlordiazepoxide, Chloral hydrate Ethchlorvynol Glutethimide Hashish Marijuana Methaqualone	Dextromethorphan Inhalants (solvents/aerosols) Ketamine Lysergic acid Diethylamide Mescaline Nitrous oxide Phencyclidine Phenylisopropylamine Methylenedioxyamphetamine Methylenedioxyethylamphetamine Methylenedioxy-methamphetamine Synthetic cathinones (bath salts)	Cyclic antidepressants Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Nortriptyline Protriptyline Trimipramine Hydroxyzine Lamotrigine Lithium Meprobamate SSRI antidepressants Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Viibryd

Briggs (2011), Hudak & Tan (2012), and Kieviet et al. (2013)

reviewed to assure that they address risk factors for prenatal drug use and addiction. Toxicology testing obtained using restricted screening criteria such as limited prenatal care, teen parent, and child protective agency involvement may overshadow identification of other important risk factors such as history of pain syndrome and use of multiple medical providers. Providers need to be aware that negative newborn toxicology screening does not rule out maternal substance abuse nor does positive screening confirm abuse or addiction (Farst, Valentine, & Hall, 2011).

Where toxicology testing is negative or unavailable, neurobehavioral screening using an abstinence assessment tool as a method to confirm substance exposure is not advocated in the literature. Elevated abstinence assessment scores are useful in guiding therapy but do not confirm NWS. In 2010, while validating an abstinence assessment tool, researchers found el-

evated scores are common among healthy, nonopioid-exposed newborns. In their study of 102 nonsubstance-exposed infants, numerous scores reached the threshold suggestive of neonatal withdrawal, particularly in infants evaluated beyond the first week of age (Zimmermann-Baer, Notzli, Rentsch, & Bucher, 2010). Results of this study have implications for interpretation of abstinence scores, especially when used to evaluate infants beyond the neonatal period.

Signs of NWS

Signs of NWS are widely variable, and reflect dysfunction in autonomic regulation, state control, and sensory and motor functioning. Signs can be broadly classified as those that impair gastrointestinal, metabolic, vasomotor, respiratory, or CNS activity (Bio, Siu, & Poon, 2011; Cramton & Gruchala, 2013; Hudak & Tan, 2012). A compilation of more specific signs of NWS can be found in Table 2.

Neurobehavioral Assessment Tools

There are several tools for assessing severity of withdrawal in term neonates, determining need and duration of pharmacologic therapy, and titration of therapies. Each of these tools produces a score that is calculated at a regular interval. The threshold score for intervention/nonintervention is specific to the assessment tool and relative to a previous score. The interval between scored assessments varies according to the assessment tool and institutional protocols (Jansson, Velez, & Harrow, 2009).

Finnegan Scoring System

One of the first scoring tools for assessing neonatal withdrawal from prenatal opioid exposure was the Finnegan tool (Finnegan, Connaughton, Kron, & Emich, 1975). The original Finnegan tool listed all recognized clinical signs of withdrawal in newborns, and semiquantified

Table 2: Signs of Neonatal Withdrawal Syndrome

Feeding and Gastrointestinal	Autonomic and Metabolic	Respiratory and Vasomotor	State, Tone, and CNS	Other
Uncoordinated suck Weak/poor suck Excessive sucking Watery/loose stools Vomiting/reflux Projectile vomiting Hyperphagia Abdominal tenderness Poor feeding/colic	Fever Temperature instability Mottling Piloerection Diaphoresis Hypoglycemia	Tachypnea Retractions Nasal stuffiness Sneezing Yawning Nasal flaring Bradycardia Tachycardia Hypertension	Lethargy Hypotonia Hypertonia Tone regulation difficulty Hyperreflexia Seizure/convulsion Tremor/jitteriness Myoclonus/clonus Opisthotonas Agitation/irritability Increased wakefulness Hyperactivity Restlessness Poor sleeping pattern Frequent/excessive crying High-pitched crying	Skin excoriation Poor weight gain Excessive weight loss High pain scores

The varied and nonspecific signs of Neonatal Withdrawal Syndrome have been described and classified in various ways. These nonspecific signs may also be associated with drug toxicity.

Bio et al. (2011), Finnegan et al. (1975), Finnegan & Kaltenbach (1992), Hudak & Tan (2012), and Kieviet et al. (2013)

CNS hyperirritability, gastrointestinal dysfunction, respiratory distress, and autonomic signs. Although novel and widely recognized, Finnegan's tool lacked specificity (Zimmermann-Baer et al., 2010).

A variety of modified Finnegan tools (e.g., M-FNAST, MOTHER NAS) have since emerged (Finnegan, 1990; Finnegan & Kaltenbach, 1992; Jansson et al., 2009). These tools remain the most often used in the United States, both in clinical practice and in research (Sarkar & Donn, 2006), although they have been validated in relatively few studies (Maguire, Cline, Parnell, & Tai, 2013). Finnegan's tools have most commonly served as the "gold standard" in research. Using the Finnegan method, an infant is assessed at regular intervals (usually every 3 to 4 hours) for specific signs and receives points for signs suggesting NWS. An infant consistently scoring eight or more using a modified Finnegan abstinence tool may require pharmacotherapy or a more committed program of nonpharmacologic therapy (See Supplemental Digital Content Figure 1, <http://links.lww.com/MCN/A20>)

Neonatal Withdrawal Inventory

In 1998, Zahorodny et al. described three studies testing a new rapid assessment tool for assessing neonatal withdrawal (Zahorodny et al., 1998). They promoted the Neonatal Withdrawal Inventory for its ease and speed of application, and because it relied upon intermittent assessment and not the use of charted data for scoring. The Neonatal Withdrawal Inventory was shown to have high interrater reliability, and high sensitivity and specificity when compared to scores obtained using a Finnegan assessment instrument.

Neonatal Narcotic Withdrawal Index

In 1981, Green and Suffet developed a tool to assess withdrawal using a sample of 50 infants with known narcotic exposure (Green & Suffet,

1981). The index contained seven elements: crying, tremors, tone, respiratory rate, temperature, vomiting, and other signs. Values of 0, 1, or 2 defined increasing intensity for each element, consistent with how severity was being scored by Finnegan. Subscores were weighted equally in developing a final score, which potentially ranges from 0 to 14. Researchers found a significant difference between scores obtained from the sample infants and control infants.

Lipsitz Tool

In 1975, Lipsitz proposed a scoring system to quantitate the clinical symptoms of the abstinence syndrome in the newborn (Lipsitz, 1975). Infants were scored on a scale of 0 to 20, with frequently occurring symptoms given highest scores. This scoring system contrasts with the severity system used by Finnegan and other researchers. Lipsitz describes a 77% incidence in identifying a narcotic-exposed infant by using the cutoff score of 4 on the tool. Although apparently simple in application, there remains a need to validate the tool's ranked system of scoring.

Ostrea System

In 1993, Ostrea described a system for evaluating abstinence in infants on the basis of manifestations that are life threatening: vomiting, diarrhea, weight loss, irritability, tremors and tachypnea. Each of these six manifestations was defined in terms of mild, moderate, and severe. Within this system, medications were used to treat and manifestation assessed as severe, or any vomiting, weight loss, or diarrhea assessed as moderate (Ostrea, 1993). Although described in both clinical and research applications, the Ostrea System has not been formally validated.

It is important for providers to recognize that the described tools used to assess withdrawal in neonates have been developed specifically for infants with NAS. Use of these tools in older infants, infants with iatrogenic

NWS, or infants withdrawing from SSRIs and other nonopioids may underestimate or overestimate the degree of withdrawal (Curley, Harris, Fraser, Johnson, & Arnold, 2006). Several pediatric withdrawal scales have been developed to evaluate opioid and benzodiazepine abstinence; however, none have been identified as valid for neonatal use (Cunliffe, McArthur, & Dooley, 2004; Curley et al., 2006; Ista, de Hoog, Tibboel, Duivenvoorden, & van Dijk, 2013; Ista, van Dijk, de Hoog, Tibboel, & Duivenvoorden, 2009).

Treatment

The goals of therapy for NWS are to ensure that the infant receives adequate nutrition and sleep in order to achieve adequate weight gain and integrate into the social environment (Hudak & Tan, 2012). This is accomplished with both nonpharmacologic and pharmacologic therapies. The threshold for initiating pharmacologic therapies is widely variable among institutions (Kellogg et al., 2011; Kuschel, 2007).

Nonpharmacologic Intervention

All substance-exposed neonates should receive individualized supportive, nonpharmacologic interventions (Velez & Jansson, 2008). This necessitates a thorough evaluation of the baby's state, behaviors, and responses to stimuli. Nonpharmacologic interventions or "comfort care" may include targeted positioning (swaddling, therapeutic tucking), soothing techniques (nonnutritive sucking, gentle rocking, massage), and interaction modifications (minimal stimulation environment) (Jansson & Velez, 2012). These techniques are routinely used prior to pharmacologic therapies for NWS, and as an adjunct to pharmacologic therapies. Intravenous hydration or small, hypercaloric feedings have been used to minimize the effects of gastrointestinal disruption, improve nutrition, and prevent dehydration (Hudak & Tan, 2012).

Breastfeeding is the preferred method of feeding for almost all term infants. For infants with methadone- or buprenorphine-dependent mothers, breastfeeding has been identified as safe, and even beneficial, regardless of dose (Abdel-Latif et al., 2006; Isemann, Meinen-Derr, & Akinbi, 2011). Breastfeeding for infants with NWS, or at risk for NWS, should be encouraged if not contraindicated because of ongoing illicit drug use or behaviors suggesting such use (Jansson, 2009). Early and ongoing involvement of a lactation consultant familiar with breastfeeding challenges associated with NWS can improve eventual breastfeeding rates for these infants, provide an additional method of calming, and improve maternal–infant attachment (Pritham, 2013). In addition, methadone and buprenorphine transferred in breast milk can effectively decrease NWS symptoms (Pritham, 2013).

Pharmacologic Interventions

There is considerable variation in the treatment of NWS across centers. Systematic literature reviews have suggested lack of high-quality evidence to support any specific medications in the treatment of NWS, although opioid treatment has now emerged as preferable to sedatives (Osborn, Jeffery, & Cole, 2005, 2010). The AAP recommends pharmacologic treatments for NWS to relieve moderate-to-severe signs and to prevent complications (fever, weight loss) in an infant who does not respond to nonpharmacologic therapies (Hudak & Tan, 2012) while recognizing that opioids generally increase length of hospital stay (Osborn et al., 2010). The most common single agent used in NWS is oral morphine, although methadone and buprenorphine are acceptable first-line choices (Cramton & Gruchala, 2013; Hudak & Tan, 2012).

Ongoing and Family Assessment

Whether infants exhibiting signs of NWS or at risk for NWS receive

inpatient or outpatient management varies across settings, and according to case-specific risk factors. Discharge from the hospital for older infants who have received opioids for NWS can be individualized in consideration of the infant's age, overall status, stability of home environment, and availability of support and follow-up (Hudak & Tan, 2012). For younger infants, it is best to delay hospital discharge until neurobehavioral assessments are free from signs of withdrawal for a period of 24 to 48 hours following discontinuation of opioids (Hudak & Tan, 2012).

Mothers have reported feeling judged by neonatal nurses and have reported feeling that an infant's abstinence scores are sometimes assigned based upon whether the nurse likes the mother (Cleveland & Gill, 2013). It has been suggested that the bond between mother and infant may become compromised if the nurse–mother relationship is strained (Cleveland & Gill, 2013). Quality of the relationship between a mother and their infant's nurse is a determinant of a mother's early mothering experience; therefore, a positive relationship should be fostered. Researchers have suggested that every reasonable effort be made to include mothers in the care of their babies, attempt communication on a personal level, and otherwise respect the dignity of these vulnerable women (Cleveland & Gill, 2013).

Conclusions and Future Directions

Incidence of fetal substance exposure is increasing, requiring improved methods for detecting, monitoring, and managing withdrawal in neonates. Extended use of opioids, barbiturates, and benzodiazepines in neonatal intensive care has resulted in iatrogenic withdrawal syndromes. Considerable variability exists in the approach to affected infants across settings. More research is needed to find better way to identify babies at

risk for NWS and optimal treatment regimens for those with NWS. Validation studies of neonatal abstinence assessment tools are needed. There is an opportunity to develop tools to aid in the assessment of withdrawal in older infants and those withdrawing from SSRIs and other nonopioids.

Clinical Implications

Each nursery should use an evidence-based protocol for the identification, evaluation, and management of neonatal withdrawal based upon best practices of the organization. The clinical team in the nursery should be educated about how to use an abstinence assessment tool, and recognize limitations of these tools for examining older infants, infants with iatrogenic NWS, and those exhibiting signs of withdrawal or toxicity from substances other than opioids. All substance-exposed neonates should receive individualized supportive, nonpharmacologic and pharmacologic interventions to ensure adequate nutrition and sleep to promote adequate weight gain and integration into the social environment. Every reasonable effort should be made to include mothers in the care of their infants, attempt communication on a personal level, and otherwise respect the dignity of these vulnerable women. ✦

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