REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Neonatal Abstinence Syndrome

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The neonatal abstinence syndrome was first described in the literature in the 1970s by Dr. Loretta Finnegan.[1] Although this syndrome has been recognized for more than four decades, there have been substantial changes in the past 10 years, including a dramatic increase in prevalence and changes in both the exposure substance and clinical management.[2,3] There has also been a considerable amount of research on the neonatal abstinence syndrome, and effective management strategies have been developed. However, gaps still exist, including a lack of clarity and consistency in how the syndrome is defined, measured, and managed. In addition, much of the research has focused on the infant in isolation from the mother, and many hospitals lack protocols to guide treatment.[4] The purpose of this review is to summarize the current literature on the neonatal abstinence syndrome, including clinical characteristics, prevention, identification, and treatment. Approaches to care that recognize the importance of the infant–mother dyad are emphasized when possible.

EPIDEMIOLOGY

The incidence of the neonatal abstinence syndrome has increased substantially in the past decade.[5-7] In 2012, the syndrome was diagnosed in 21,732 infants in the United States,[6] which represents an increase by a factor of 5 during the previous 12 years.[5] This is consistent with the increased prevalence of the neonatal abstinence syndrome in other locations, including England, Canada, and Western Australia,[8] and reflects an increasing global problem. The increase in cases of the neonatal abstinence syndrome corresponds with the reported rise in opioid use during pregnancy,[9-11] which is attributed to the more liberal use of prescribed opioids for pain control in pregnant women,[12-14] illicit use of opioids such as oxycodone and heroin,[15,16] and a dramatic increase in opioid-substitution programs for the treatment of opioid addiction.[17] The pattern of opioid use has also shifted from an inner-city, low-income population to a more socioeconomically and demographically diverse population that includes pregnant women.[10,18] The causes of the neonatal abstinence syndrome are similarly diverse, including in utero exposure to prescribed or illicit opioids and to agents used for the treatment of maternal opioid addiction.

Research on opioid use during pregnancy has documented the negative effects on the pregnant woman, fetus, and neonate (Table 1).[19-25] Illicit opioid use is often complicated by a chaotic lifestyle that includes drug-supporting and drug-seeking behaviors.[21] This lifestyle may hinder access or commitment to medical and social services,[26] leading to substantial risks of illness and death. These risks can be mitigated with opioid-substitution treatment, which has benefits for both health and social outcomes.[19,21] Methadone is currently the most commonly prescribed treatment for opioid addiction during pregnancy,[27] although the evidence suggests

Table 1. Clinical and Other Consequences of Maternal Opioid Use.*

Outcomes in the pregnant woman
Sexually transmitted infections
HIV infection
Hepatitis
Endocarditis
Osteomyelitis
Sepsis
Cellulitis
Chaotic lifestyle (e.g., prostitution, violence, and theft)
Decreased commitment to health care
Decreased receptiveness to social services
Outcomes in the fetus
Growth restriction
Abruptio placentae
Preterm labor
Abnormal heart patterns
Death
Outcomes in the newborn
Low birth weight
Preterm delivery
Small head circumference
Sleep myoclonus
Child maltreatment
Visual disturbances

* The information provided in the table is from Wong, Ordean, and Kahan,[19] Patrick et al.,[20] the ACOG Committee on Health Care for Underserved Women,[21] Visconti et al.,[22] Jansson and Velez,[23] Lee et al.,[24] and O'Donnell et al.[25]

that buprenorphine may be associated with less severe neonatal withdrawal than methadone.[28-30] Regardless of whether the fetus is exposed to prescribed or illicit opioids, the neonatal abstinence syndrome is a prevalent outcome.

TERMINOLOGY

The neonatal abstinence syndrome refers to a postnatal opioid withdrawal syndrome that can occur in 55 to 94% of newborns whose mothers were addicted to or treated with opioids while pregnant.[1,27] Other terms have also been used to describe the syndrome, including the neonatal withdrawal syndrome,[25] the neonatal drug withdrawal syndrome,[8] and neonatal withdrawal.[27] Although the neonatal abstinence syndrome is the term used most frequently in the literature, neonatal withdrawal is probably a more accurate description of the syndrome, since abstinence implies an intention to abstain, and neonates lack the capacity for such an intention.

Some researchers have used a more liberal definition of the neonatal abstinence syndrome that includes exposure to nonopioid substances. This can be problematic because the assessment tools for the neonatal abstinence syndrome were developed for infants exposed to opioids.[31] However, polysubstance use is common among those who use opioids,[10,32] and it is not always possible to attribute the cause of the neonatal abstinence syndrome to exposure to opioids alone.

The inconsistent terminology can lead to challenges in understanding the magnitude and complexity of the syndrome, the presenting signs, and the most effective treatment strategies.[17] In this review, we focus on the neonatal abstinence syndrome as a result of opioid exposure, recognizing that many cases involve the use of one or more substances in addition to opioids, which may complicate the evaluation and treatment of the syndrome.[33]

CLINICAL FEATURES AND OUTCOMES

The neonatal abstinence syndrome has been described as a complex disorder that primarily involves the central and autonomic nervous systems and the gastrointestinal system.[3,11] The clinical manifestations of the syndrome vary (Table 2),[1,34,35] ranging from mild tremors and irritability to fever, excessive weight loss, and seizures. Clinical signs typically develop within the first few days after birth, although the timing of their onset, as well as their severity, can vary.[3] This variation is poorly understood and is believed to be multifactorial.[11,39] In particular, the type of opioid and the dose and timing of exposure may alter the risk of withdrawal.[40] Clinical manifestations may develop later in infants who have been exposed to opioids with a longer half-life (e.g., methadone and buprenorphine) than in infants exposed to short-acting opioids.[3] Exposure to additional substances, such as selective serotonin-reuptake inhibitors (SSRIs), benzodiazepines, and nicotine, may also alter the onset of the syndrome, as well as the severity of symptoms.[20,31] Furthermore, other variables may influence the

Table 2. Clinical Manifestations and Outcomes of the Neonatal Abstinence Syndrome.*

Metabolic, vasomotor, and respiratory manifestations
Fever
Frequent yawning
Sneezing
Sweating
Nasal stuffiness
Respiratory rate >60 breaths per minute, with or without retractions
Mottling
Tachypnea
Gastrointestinal manifestations
Projectile vomiting
Regurgitation
Loose or watery stools
Weight loss
Poor feeding
Excessive sucking
Central nervous system manifestations
Tremors
High-pitched crying
Sleep disturbances
Increased muscle tone
Excoriation
Myoclonic jerks
Irritability
Seizures
Outcomes
Admission to neonatal intensive care unit
Pharmacologic treatment for 60–80% of infants
Prolonged hospitalization (average, 17 days)
Increased risk of birth complications (e.g., low birth weight, jaundice, and feeding difficulties)
Disrupted bonding
Child-safety concerns

* Data on manifestations are from Finnegan et al.,[1] Newnam et al.,[34] and D'Apolito,[35] and data on outcomes are from Patrick et al.,[5,6] Jansson and Velez,[23] Lee et al.,[24] Uebel et al.,[36] Cleary et al.,[37] and Wachman et al.[38]

development of the neonatal abstinence syndrome, including maternal factors (poor nutrition or stress), placental opioid metabolism, genetic variables, neonatal conditions (prematurity or infection), and environmental factors such as the early care that neonates receive (extent of stimulation and rooming-in vs. care in a nursery).[11,39,41,42] With these considerations in mind, the typical hospital stay of 24 to 48 hours for term neonates should be extended for opioid-exposed neonates. The American Academy of Pediatrics has recommended that opioid-exposed neonates be observed for 3 to 7 days before discharge,[27] whereas recent evidence suggests that a period of 5 days is adequate.[43]

Infants with the neonatal abstinence syndrome are at increased risk for admission to the neonatal intensive care unit,[7,36,37] birth complications,[6] the need for pharmacologic treatment,[7,23] and a prolonged hospital stay[24,38] (Table 2), outcomes that separate the mother and her infant at a critical time for infant development and bonding. The average length of stay for infants with the neonatal abstinence syndrome is 17 days overall and 23 days for those requiring treatment.[6] Prolonged hospitalization results in the use of a greater portion of health care resources for the care of infants with the neonatal abstinence syndrome[5] than for those without the syndrome.

PREVENTION

Primary-prevention strategies are needed to address the epidemic of opioid use and the associated development of the neonatal abstinence syndrome. Ongoing surveillance is essential to inform public health–related efforts aimed at prevention.[14] Evidence suggests that in the United States, states with the highest rates of prescription opioid use also have the highest rates of the neonatal abstinence syndrome.[6] Therefore, targeted initiatives to address prescribing practices may help to reduce opioid use in women of childbearing age and prevent the subsequent development of the neonatal abstinence syndrome.[11] Efforts are under way to address the overprescribing of opioids, such as the introduction of programs to monitor opioid-drug prescribing practices, regulation of pain-management clinics, and establishment of opioid dosage thresholds.[44] Health care providers are encouraged to practice safe and judicious prescribing of opioids to women of childbearing age. Since various medications, such as SSRIs and benzodiazepines, can exacerbate signs of the neonatal abstinence syndrome,[17,20] the risks and benefits of all medications taken during pregnancy

should be evaluated, with subsequent education provided for pregnant women who use substances associated with the syndrome. In addition, smoking-cessation strategies should be offered to women who smoke.[19,31] Since few jurisdictions have substance abuse treatment programs specifically designed for pregnant women, establishing such programs and increasing the accessibility of methadone treatment may also help to prevent the neonatal abstinence syndrome.[45] Punitive legislation for women using substances during pregnancy should be discouraged, since negative consequences of disclosing substance use may prevent women from seeking prenatal care.[45] All these suggested interventions should be part of a program of comprehensive care that is sensitive to the needs of women who use substances that are associated with the neonatal abstinence syndrome.

IDENTIFICATION OF INFANTS AT RISK

MATERNAL HISTORY

Identification of infants at risk for the neonatal abstinence syndrome is important to ensure accurate clinical assessment, promote early intervention, and mitigate signs of withdrawal in the newborn.[46,47] However, many women are reluctant to divulge substance use because of the social and legal consequences.[27,48] A recent systematic review of "relational care" showed that engagement with perinatal services for women who use substances is improved when clinicians establish respectful, empathic, and collaborative relationships with patients.[49] Thus, the use of a nonjudgmental and open-ended approach to interviewing all pregnant women (versus only those with risk factors) about substance use during pregnancy, while encouraging them to report substance use, is recommended to facilitate disclosure.[19,21] In the absence of maternal self-report, assessment tools are available to assist practitioners in identifying substance use during pregnancy[10]; however, the effectiveness of the tools may be enhanced when they are used in a nonjudgmental manner.

TOXICOLOGIC TESTING

In addition to self-report, results of biologic testing of the pregnant woman or the newborn can ensure accurate assessment of substance exposure and can guide treatment.[27,50] Evidence suggests that when biologic specimens are tested for the presence of drugs, the rate of positive results is higher than the rate of self-reported substance use.[51] Toxicologic testing of the pregnant woman requires her consent, whereas there is no consistent policy regarding maternal consent for biologic testing in the neonate.[19,51] Health care providers should be aware of the specific policy in their practice setting. Furthermore, recommendations regarding universal versus targeted screening are lacking.[52] The primary advantage of universal screening over targeted screening is increased sensitivity and specificity.[50] Targeted screening enables identification of women at highest risk and is believed to be more cost-effective than universal screening.[52,53]

Biologic specimens from the neonate include meconium, hair, cord blood, and urine.[51] Each method of toxicologic testing is beneficial in identifying substance exposure in the newborn, but the tests have limitations, including the timing of sample collection and the period of detection of drug exposure (Table 3).[51,54,55] Thus, although testing of biologic samples is useful for increasing the detection of substance exposure, it should be considered an adjunct to clinical assessment. A multimethod approach to identifying infants at risk for the neonatal abstinence syndrome and a protocol for newborn screening are recommended for consistency and accuracy.[27]

ASSESSMENT TOOLS

The objective assessment of newborns who have signs of the neonatal abstinence syndrome is essential for quantifying the severity of signs and symptoms, providing guidance for pharmacologic treatment, and facilitating structured weaning.[34,56] Several tools are available to aid in the assessment of newborns for the syndrome, each with strengths and limitations[34,56,57] (Table 4). The Finnegan Neonatal Abstinence Scoring Tool is the most widely used assessment tool[35] in either its original 1975 format[1] or a modified version as recommended by the American Academy of Pediatrics.[27] Critiques of the original Finnegan tool point to its complexity, with too many items for practical use.[56] Thus, the modified version was developed for practicality and ease of use.[27,62,63] However, one concern is that there have been many adaptations of the modified tool, and no single modified version has been applied univer-

Table 3. Biologic Testing in the Neonate.*

Biologic Specimen	Period of Detection	Collection Procedure	Special Considerations
Urine	Detects drug exposure within the last few days of fetal life	Immunoassay screening, noninvasive bag specimen collection	Efficient sample collection is necessary because the first urine specimen is the most highly concentrated; false negative results are possible because of drugs clearing rapidly from the urine and dilute urine samples.
Meconium	Detects drug exposure from the beginning of the second trimester	0.5-g stool sample collected and stored at –20°C to –80°C before drug measurement by means of organic-solvent extraction	Sample collection before contamination with human milk or formula yields most accurate results; avoid contamination with urine; specimen collection is difficult in neonates who have passed meconium in utero; results take time because a laboratory is used in most cases.
Hair	Detects drug exposure from the beginning of the third trimester	20 to 50 mg of hair cut close to the scalp required for adequate testing; stored at room temperature	Samples may be collected for several months after birth; method of detection is limited with insufficient hair sample; can be used to estimate approximate exposure period.
Cord blood	Detects drug exposure in the last few hours or days of fetal life	Sample of cord blood obtained from umbilical cord at time of birth	Testing is less sensitive than testing of other specimens because drug concentrations are lower.

* Data are from Cotten,[51] Farst, Valentine, and Hall,[54] and Lozano et al.[55]

sally. Overall, the subjectivity of the existing assessment tools is also of concern,[31] and their reliability and validity vary.[57] Although original research indicates that existing tools are valid,[1,58-60] specific psychometric properties of the tools have not been published, with the exception of the MOTHER NAS Scale[57] and the Finnegan Neonatal Abstinence Syndrome Scale — Short Form.[61] However, the findings for these tools were limited, and neither one has been identified as superior. Continued tool development is required.

Regardless of the scoring tool that is used, protocols for its use are required and should include training for staff members who perform newborn assessments.[27] An interobserver reliability rate of 90% or greater is recommended among health care providers completing assessments.[35] This is of particular importance for health care providers working in organizations that do not frequently observe infants with withdrawal and for new staff members who lack familiarity with the assessment of infants who have the neonatal abstinence syndrome. Despite these recommendations for practice, many organizations do not have screening protocols in place, and training materials are often lacking.[27,56]

MANAGEMENT

The primary concerns regarding management of the neonatal abstinence syndrome are to promote normal growth and development and to avert or minimize negative outcomes, including discomfort and seizures in the infant and impaired maternal bonding.[41] Overall, guidelines are lacking regarding nonpharmacologic care, since there have been no large, high-quality, randomized, controlled trials evaluating nonpharmacologic treatment of the neonatal abstinence syndrome.

Ideally, care should be multidisciplinary, collaborative, nonjudgmental, and based on the identified needs of the infant–mother dyad so that care of the infant does not occur in isolation from the mother.[39,64] Creating a compassionate, safe environment for the mother is important, since many mothers feel stigmatized and guilty regarding substance use and the neonatal abstinence syndrome, which can lead to impaired communication with health care providers. The mother's participation in the care of her affected

Table 4. Assessment Tools to Guide Pharmacologic Treatment of the Neonatal Abstinence Syndrome.*

Tool and Year Tool Published	No. of Items	Score Range	Score for Treatment	Published Item Definitions	Interobserver Reliability Established	Training Materials or Formal Course Available	Strengths and Limitations
Finnegan Neonatal Abstinence Scoring Tool (1975)[1]	21	0–62	≥8 on three consecutive evaluations	Yes	Yes	Training manual available as online video or DVD	Is the seminal and most widely used scoring tool; is frequently modified, causing confusion among clinicians; has a length and complexity that make it less practical to use than other tools; has an internal consistency[57] (Cronbach's alpha) that does not exceed 0.62
Lipsitz Neonatal Drug Withdrawal Scoring System (1975)[58]	11	0–20	≥4	No	No	No	Has a moderate number of items for scoring; involves simplicity and sensitivity of scoring; does not address reliability; has no item definitions provided with the tool; has no available training materials
Neonatal Narcotic Withdrawal Index (1981)[59]	7	0–14	≥5 on two evaluations in 24 hr	Yes	Yes	No	Is a simple tool with limited number of items for scoring; has a high level of interobserver reliability; has no available staff education and training module
Neonatal Withdrawal Inventory (1998)[60]	7	0–19	≥8	No	Yes	No	Is rapidly administered because of the small number items for scoring; has high sensitivity, specificity, and interobserver reliability; has no available staff education and training module
MOTHER NAS Scale (2010)[28]	19	0–42	9; rescore before initiation of drug treatment	Yes	Yes	Video developed for training of multicenter research staff only	Is a modified version of Finnegan Neonatal Abstinence Scoring Tool with redundancies removed and two items added for specificity; includes instruction for nursing staff and a protocol for pharmacologic treatment; has high interobserver reliability; has no available staff education and training module; has an internal consistency[57] (Cronbach's alpha) that does not exceed 0.62
Finnegan Neonatal Abstinence Syndrome Scale — Short Form (2013)[61]	7	0–16	≥8	Yes†	Yes	No‡	Involves rapid assessment with limited items for scoring; has strong correlation with original Finnegan tool according to factor analysis[61]; may be inadequate to assess neonates with rapidly escalating signs and symptoms of withdrawal; requires further testing before widespread use

* The data provided in the table are based on overviews and comparisons of the various assessment tools reported by Newnam et al.[34] and Orlando,[56] as well as specific assessments of each tool, which are cited in the table.
† Some definitions are the same as those in the original Finnegan tool (Finnegan Neonatal Abstinence Scoring Tool[1]).
‡ Training materials from the original Finnegan tool may be used.

infant has the potential to benefit both mother and infant, with improvement in the manifestations of the syndrome and enhanced bonding and parenting.[17,65] Although many mothers are able to provide consistent care for the neonate, a comprehensive psychosocial assessment of the family is needed to ensure adequate support and safety of the newborn. If maternal participation is compromised, efforts should be made to engage the family in the plan of care. If there is concern about the safety of the neonate that requires a report to child protective services, clinicians are encouraged to promote open dialogue in a collaborative approach involving health care team members, the mother, and child protective services, with the goals of ensuring the child's safety and providing psychosocial support for the family.

SUPPORTIVE CARE

The initial care of all infants who have been exposed to substances in utero should be individualized, supportive, and nonpharmacologic.[17,39] This approach involves creating a gentle, soothing environment with minimal stimulation in an effort to calm and soothe the infant.[3,11] The current standard care for opioid-exposed infants involves limiting exposure to lights and noise, promoting clustering of care to minimize handling and promote rest, swaddling and holding the infant, and providing opportunities for non-nutritive sucking.[4,66] Adequate nutrition to minimize weight loss should also be part of the initial therapy.[27] For infants who have inadequate weight gain, an increase in the frequency of feedings with high-calorie, lactose-free formula may be required to mitigate some of the effects of the neonatal abstinence syndrome, including increased energy expenditure, reflux, vomiting, and diarrhea.[27,40] Additional supportive interventions include music therapy, massage, use of a water bed, and recruitment of volunteers to cuddle the infant.[66]

Although soothing techniques are commonly used to comfort infants, these interventions have not been evaluated in relation to such outcomes as the severity of the neonatal abstinence syndrome or the length of the hospital stay.[31] The strongest evidence from systematic reviews for improving outcomes is in support of breast-feeding, with emerging evidence that favors rooming-in.[4,66] Studies have consistently shown that infants with the neonatal abstinence syndrome who are breast-fed tend to have less severe symptoms, require less pharmacologic treatment, and have a shorter length of stay than formula-fed infants.[42,67-69] Breast-feeding should therefore be encouraged for mothers who are stable and receiving opioid-substitute treatment,[70,71] unless there are contraindications, such as human immunodeficiency virus infection or concurrent use of illicit substances. Similarly, emerging evidence suggests that infants who stay in the room with their mothers have a shorter hospital stay and duration of therapy and are more likely to be discharged home with their mothers.[4,72,73] Rooming-in has also been associated with improved breast-feeding outcomes,[74] enhanced maternal satisfaction,[75] and greater maternal involvement in the care of the newborn.[66]

Despite the benefits of breast-feeding and rooming-in with respect to outcomes of the neonatal abstinence syndrome, there are barriers to the implementation of these recommendations. Among mothers receiving opioid-replacement treatment, breast-feeding rates remain low[74,76] because of difficulties with infant feeding,[67] separation of the newborn from the mother resulting from admission to special care nurseries, lack of encouragement from health care providers who are unaware of the benefits of breast-feeding during opioid-replacement treatment,[77] and concerns regarding neonatal sedation or adverse effects.[78] Similarly, institutional limitations such as lack of funding, lack of personnel, poor design of hospital units, and reluctance to introduce practices based on new evidence may prevent many hospitals from providing rooming-in as a standard practice.[66] These barriers need to be addressed, since current practices may be hindering progress in improving outcomes.

PHARMACOLOGIC TREATMENT

Pharmacologic treatment is an important component of management when nonpharmacologic care is insufficient to mitigate signs and symptoms of the neonatal abstinence syndrome. Approximately 60 to 80% of infants with the syndrome do not have a response to nonpharmacologic treatment and require medication.[3] The main objective of pharmacologic treatment is to relieve moderate-to-severe signs such as seizures, fever, and weight loss or dehydration.[27] Despite the importance of pharmacologic treatment, there is no universally accepted standard of care, and variations exist in current practice[79,80] regarding the use of doses based on weight or symptoms,

as well as the threshold for initiating treatment, starting doses, weaning protocols, and adjunctive medications.[17,81]

There is current consensus in practice that first-line pharmacotherapy consists of opioid replacement with either oral morphine solution or methadone.[27,82] Oral morphine is the most common treatment in the United States.[11] Morphine is a full mu-opioid receptor agonist with well-established pharmacokinetic features and a short half-life, which may facilitate dose adjustment.[3,40] Methadone is a synthetic full mu-opioid–receptor agonist with a longer half-life (25 to 32 hours), which may provide a more consistent blood concentration over time and result in less frequent dosing.[40] The disadvantages of each medication must also be considered. Morphine is associated with increased risks of sedation and respiratory depression and a prolonged hospital stay, and methadone contains ethanol.[3,41]

Recent evidence suggests that the use of a standardized protocol for pharmacologic treatment of the neonatal abstinence syndrome may be more important than the choice of drug[41,79,83] (Table 5). Hall and colleagues[79] found that, regardless of the opioid used for treatment, infants who underwent protocol-specified weaning had significantly fewer treatment days and a shorter length of stay than infants who were weaned without the use of a protocol. Similarly, Patrick and colleagues[84] found that improved standardization of care through participation in a quality-improvement collaboration led to a shorter duration of pharmacologic treatment, a reduced length of stay, and a smaller number of infants who were receiving medication at the time of discharge. In addition, evaluation of a revised protocol for methadone weaning based on a pharmacokinetic model for oral methadone[85] showed that infants who received treatment according to the revised protocol had a shorter duration of methadone treatment and a shorter hospital stay, as compared with infants who underwent standard weaning.[86] Overall, these findings suggest that decisions regarding pharmacologic treatments should be based on protocols,[79,84,86] since they may have the greatest effect on neonatal outcomes. These recent studies are noteworthy contributions to the literature, given that efforts to reduce length of stay have not been successful for the past several years.[6]

Emerging evidence exists regarding the effects of sublingual buprenorphine to treat infants who have the neonatal abstinence syndrome. As compared with morphine, buprenorphine, a partial agonist, has been associated with significant reductions in the duration of treatment (23 days vs. 38 days) and of hospitalization (32 days vs. 42 days).[87] Similarly, sublingual buprenorphine was found to be superior to methadone in a recent cohort study.[88] Infants treated with buprenorphine had a significantly shorter course of treatment and decreased hospital stay, as compared with infants who received methadone. Given these findings, as well as current evidence of the effectiveness of buprenorphine for the treatment of opioid addiction in pregnancy and potentially less severe neonatal withdrawal,[80] the benefits of treatment with buprenorphine look promising. Moreover, a pharmacokinetic model exists for buprenorphine, which may assist in the development of an evidence-based dosing protocol.[89] However, since buprenorphine contains a substantial amount of ethanol, safety is a primary concern.[41] Safety issues, lack of efficacy, and side effects have led to recommendations against treatment with paregoric, tincture of opium,[39,90] or diazepam[81,91] for infants with the neonatal abstinence syndrome.

Adjunctive second-line agents may be considered if the infant does not have a response to monotherapy regimens.[40] Specific guidelines are lacking on when to add second-line agents, and diverse situations in practice are often observed. Phenobarbital, a long-acting barbiturate, and clonidine, an α_2-adrenergic agonist, have been identified as second-line agents that may be useful in reducing the severity of the neonatal abstinence syndrome.[91] Phenobarbital has several disadvantages. It is not effective for gastrointestinal manifestations of the syndrome, it results in central nervous system depression and impairment of the sucking reflex, and it has a prolonged half-life (45 to 100 hours).[33] Limited data from a systematic review suggest that clonidine may be as effective as an opioid in the treatment of the neonatal abstinence syndrome.[92] This finding provides some optimism regarding the potential for a non-narcotic treatment option; however, further evaluation must be completed before clonidine can be recommended as monotherapy.[40]

OUTPATIENT WEANING

We are unaware of any data from randomized studies regarding outpatient weaning of infants from pharmacologic treatment of the neonatal

Table 5. A Standardized Treatment Protocol for the Neonatal Abstinence Syndrome.*

Protocol Component	Description	Comments
Nonpharmacologic treatment	Involves swaddling, comfort, and feeding.	Provide decreased stimulation, swaddling, continuous holding, and frequent feeding; encourage breast-feeding if mother is in active treatment; if mother is not breast-feeding, consider frequent feedings with nonlactose formula containing 22 cal per ounce.
Treatment with morphine or methadone	Initiate if score on a modified version of the Finnegan Neonatal Abstinence Scoring Tool† is >8 on two occasions or if one score is ≥12; dose of either drug: 0.05 mg per kilogram, administered orally.	Use scoring tool every 3 hr before feeding; provide refresher training in scoring system for nurses performing assessments; each center should choose either morphine or methadone as the standard pharmacologic treatment for all affected infants; see specific dosage protocols in the full protocol, since the frequency of administration differs for morphine versus methadone.
Dose escalation	If score >12, increase dose by 0.02 mg per kilogram.	Adjust the dose to the score as specified by protocol.
Stabilization	Maintain dose for 48 hr.	All scores should remain ≤8 for minimum of 48 hr.
Weaning	Reduce stabilization dose by 10% every 24 hr; discharge 48 hr after withdrawal of morphine or 72 hr after withdrawal of methadone.	Begin weaning after 48 hr of stabilization on the same dose.

* This is a modified version of the protocol developed by the Ohio Children's Hospitals Neonatal Research Consortium.[83]
† A modified version of the Finnegan Neonatal Abstinence Scoring Tool has been recommended by the American Academy of Pediatrics.[27]

abstinence syndrome or guidelines to support this practice. The majority of infants receive inpatient treatment, but in some cases, a combination of inpatient and outpatient treatment may be used.[41] Several factors need to be considered regarding an adequate setting for weaning, including neonatal safety and cost-effectiveness.[81] Although outpatient weaning shortens the hospital stay and reduces the financial burden on the health care system, infants often have a longer duration of treatment because weaning is typically less aggressive in the outpatient setting.[93,94] However, Smirk and colleagues[95] found no increase in total treatment time. Since the long-term effects of prolonged opioid exposure for infants with the neonatal abstinence syndrome are unknown, the choice between inpatient and outpatient treatment should be based on an evaluation of benefits and risks.[33,40]

MANAGEMENT OF LONG-TERM OUTCOMES

The long-term neurodevelopmental outcomes of the neonatal abstinence syndrome are more difficult to ascertain than short-term outcomes, given the numerous confounding environmental and social factors associated with substance-using mothers. Recent population-based research presents compelling evidence of adverse outcomes throughout childhood, such as maltreatment, mental health and behavioral problems, and visual disorders, which suggest a need for early intervention aimed at both infants and their caregivers.[36] Thus, medical follow-up care and social services after discharge from the hospital are recommended to ensure child safety and promote healthy development.[27,66] The complexity of the neonatal abstinence syndrome calls for service collaboratives that include early-intervention programs, child protective services, and health care services, an approach that may lead to improvements in outcomes for those affected by the syndrome.[84]

CONCLUSIONS

The increased incidence of the neonatal abstinence syndrome and soaring increases in associated health care costs warrant a consistent and comprehensive approach to mitigating the negative outcomes for affected infants, their mothers, and the health care system. Recent innovations in management include standardized protocols

for treatment, which have positive effects on important outcomes such as the duration of opioid treatment, the length of the hospital stay, and the use of adjunctive drugs. In addition, evidence from pharmacokinetic models supports the development of empirically based dosing protocols. Breast-feeding and rooming-in are promising nonpharmacologic strategies that may also improve outcomes for infants and mothers, including maternal satisfaction with and involvement in the care of the newborn. However, there are barriers to the implementation of these practices. Rigorous research is needed to provide evidence supporting the development of protocols, including a validated, standardized assessment tool and evidence-based guidelines for nonpharmacologic and pharmacologic treatment. More research is also needed on drugs, including clonidine and buprenorphine, for the treatment of affected infants and on alternative methods of care, such as outpatient weaning from pharmacologic treatment of the neonatal abstinence syndrome.

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