Neonatal Abstinence Syndrome: Presentation and Treatment Considerations

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The increase in opioid use among the general population is reflected in pregnant women and neonatal abstinence syndrome (NAS) statistics. This increase has produced an unprecedented focus on NAS from both the political-judicial sphere and the medical community. Under the banner of fetal protection, judges and prosecutors have implemented punitive approaches against women who use prescribed and nonprescribed opioids during pregnancy, including arrest, civil commitment, detention, prosecution, and loss of custody or termination of parental rights. Within the medical community, questions have been raised regarding protocols to detect prenatal drug exposure at delivery, NAS treatment protocols, the need for quality-improvement strategies to standardize care and reduce length of stay for mother and infant, and the benefits of engaging the mother in the care of her infant. It is not uncommon for the expression of strong discordant views on these issues both between and among these political-judicial and medical constituencies. Closely examining the issues often reveal a lack of understanding of substance use disorders, their treatment, and the occurrence and treatment of NAS. This study provides an in-depth examination of NAS, including variations in presentation and factors that impact the efficacy of treatment, and also identifying questions that remain unanswered. Finally, 4 key areas on which future research should focus to guide both medical care and public policy are discussed.

Key Words: neonatal abstinence syndrome, public policy, treatment

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Prescription opioid use and misuse have significantly increased within the past decade (SAMHSA, 2013). Women who use or misuse opioids and become pregnant are not protected from this increase; thus, there has been a corresponding increase in the occurrence of neonatal abstinence syndrome (NAS) (ie, manifestation of opioid-withdrawal signs and symptoms postbirth after the discontinuation of prenatal opioid exposure) (Patrick et al., 2012). This increase has produced an unprecedented focus on NAS from both the political-judicial sphere and the medical community. This focus calls into question the possible risks of fetal harm due to substance exposure, and questions the ability of women who use both licit and illicit substances to adequately parent their child (Terplan et al., 2015). Under the banner of fetal protection, both senate and house bills (ie, Protecting Our Infants Act of 2015) have directed federal agencies to provide recommendations for the diagnoses and treatment of infants undergoing NAS. State government policy-makers have crafted legislation requiring NAS prevalence surveillance and even criminalizing in utero drug exposure in both prescribed and illicit forms. For example, Tennessee implemented statewide mandatory NAS surveillance reporting in 2013 and passed law SB1391 in 2014 criminalizing adverse pregnancy outcomes due to prenatal drug exposure. Under this same banner of fetal protection, Alabama and South Carolina's State Supreme Courts have both authorized the prosecution of pregnant women for drug use. Further, judges and prosecutors have implemented punitive approaches against women who use prescribed and nonprescribed opioids during pregnancy, including arrest, civil commitment, detention, prosecution, and loss of custody or termination of parental rights (Terplan et al., 2015). Within the medical community, questions have been raised regarding protocols to detect prenatal drug exposure at delivery, NAS treatment protocols (Hudak and Tan, 2012), the need for quality-improvement strategies to standardize care and reduce length of stay for mother and infant, and the benefits of engaging the mother in the care of her infant (Vermont Oxford Network, 2013). It is not uncommon for the expression of strong discordant views on these issues both between and among these political-judicial and medical constituencies. Closely examining the issues often reveals a lack of understanding of substance use disorders, their treatment, and the occurrence and treatment of NAS. The purpose of this study is to provide an in-depth examination of NAS, including variations in presentation and factors that impact the efficacy of treatment, and also identifying questions that remain unanswered.

NAS History

Neonatal abstinence syndrome is the occurrence of opioid withdrawal at birth after the discontinuation of opioid

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exposure in utero. It is characterized by signs and symptoms of central nervous system hyperirritability, including excessive crying, increased muscle tone, tremors and sleep disturbance; gastrointestinal dysfunction including poor feeding, vomiting, and diarrhea; respiratory distress; and autonomic symptoms including sweating, sneezing, and mottling (Finnegan and Kaltenbach, 1992). The first reported case of NAS was in 1865, and the first treated NAS case was reported in 1903 (Kocherlakota, 2014). NAS was initially called congenital morphinism, and subsequently has been referred to as narcotic abstinence and/or neonatal abstinence for over 50 years. A major focus on NAS emerged during the 1950s and the early 1960s as a heroin epidemic emerged and methadone for the treatment of heroin dependence was initiated (Jones and Fielder, 2015). In the 1970s, numerous publications described the perinatal implications of heroin use and outcomes of infants born to women treated with methadone, NAS treatment regimens, and assessments designed to guide diagnosis and treatment of NAS. When methadone-assisted treatment was first approved, the Federal Drug Administration (FDA) mandated that pregnant women could not receive it and maintained women who became pregnant must be discontinued from it. However, this mandate was quickly reversed after a set of case reports showing fetal harms as a result of such discontinuation (Blinick et al., 1969; Blinick et al., 1976; Jones et al., 1999). Methadone was then recommended for pregnant opioid-dependent women, and the more than 40 years of published literature contains studies related to prenatal methadone exposure and NAS. Current evidence-based guidelines recommend that maternal dose should be individualized based on clinical indications; should not be kept low to avoid NAS; may need to be increased as gestation progresses; and taper/withdrawal during pregnancy should be avoided (SAMHSA, 2005; ACOG, 2012; World Health Organization, 2014).

In 1997, clinical guidelines for the management of chronic pain expanded opioid use in the general US population, and pain medication manufactures aggressively marketed opioid medications to hospitals, providers, and the public (American Society of Anesthesiology, 1997). Since that time, prescription opioid use and misuse has increased, and that increase is reflected in pregnant women and NAS statistics. For example, maternal opioid use increased from 1.19 per 1000 hospital births in 2000 to 5.63 per 1000 hospital births in 2009, with similar increases in the incidence of NAS of 1.20 to 3.39 per 1000 live births (Patrick et al., 2012). Subsequent studies focusing on state data for Washington (Creanga et al., 2012); Tennessee (Warren et al., 2015); and Florida (Lind et al., 2015) have reported even larger increases of NAS. These studies launched the consideration of NAS as an epidemic that requires public health surveillance and government intervention to protect children from mothers. However, these studies are all based on NAS hospital codes and are unable to differentiate NAS resultant from maternal opioid abuse and the legitimate use of an opioid prescription, which present very different contexts with often very different outcomes. Additionally, the codes neither reflect whether an infant required treatment for NAS nor what the variations in treatment may have done to exacerbate or minimize lengths of stay and corresponding hospital costs. In other countries, it is noted that NAS could be significantly under-reported where NAS is only coded if pharmacological treatment is received.

NAS and Nonopioid Exposure

Neonatal abstinence syndrome originally specified prenatal opioid exposure; the signs and symptoms defining NAS are opioid exposure-specific; and all published NAS assessment tools have been designed only to assess opioid exposure, with the exception of a recent tool developed to assess opioid and benzodiazepine withdrawal (Franck et al., 2008). In the early 1970s, when NAS was a focus, the term morphed from narcotic abstinence into neonatal abstinence. Recently, the Substance Abuse Mental Health Administration (SAMHSA) has suggested the use of the term neonatal opioid withdrawal syndrome (NOWS) to ensure its reference to opioids only.

Withdrawal similar to opioid exposure and requiring treatment has been described in the 1970s in small samples of infants prenatally exposed to alcohol (Pierog et al., 1977), benzodiazepines (Rementeria and Bhatt, 1977), and barbiturates (Desmond et al., 1972). It is unclear if these findings represent current context of treatment for these 3 exposures.

The convergence of the need to use a withdrawal-assessment tool and a shift in drug use patterns from heroin to cocaine/crack in the 1980s to 1990s led to the ''diagnosis'' of NAS for nonopioid drug exposure, creating confusion and misunderstanding. Mothers often used both crack and opioid(s), and when newborns exhibited NAS, there was little to no differentiation as to whether it was the result of prenatal opioid exposure, cocaine exposure, or both.

Selective serotonin reuptake inhibitors (SSRIs) seem to produce signs/symptoms similar to opioid withdrawal and may represent a serotonin syndrome due to increased serotonin concentration (Hudak and Tan, 2012). Unless the exposure is concomitant with prenatal opioid exposure, symptoms usually do not require treatment (Kieviet et al., 2013).

NAS PRESENTATION

The presentation of NAS is quite variable in terms of timing, symptoms, severity, and duration, and as such requires a thorough understanding of the differences that occur to ensure appropriate treatment.

Timing of Presentation

Onset of presentation varies both within and between specific opioids. NAS from prenatal heroin exposure usually occurs within 24 to 48 hours, with most infants exhibiting symptoms within the first 12 to 24 hours (Zelson et al., 1971). NAS due to methadone exposure typically occurs between the first 48 and 72 hours with NAS onset after prenatal buprenorphine somewhat later than methadone (Jones et al., 2010b). For example, in a secondary analysis of double-blind study data, the mean time to treatment for the buprenorphine group was 22 hours longer than the methadone-exposed infants (65 h 56 mo vs 43 h 53 mo, respectively) (Gaalema et al., 2012). In a subsequent retrospective chart review, similar differences in mean time to treatment for buprenorphine and methadone (73 h 10 mo vs 42 h 36 mo, respectively) were found (Gaalema et al., 2013). Currently, there are no

systematic studies of time of onset of NAS in infants prenatally exposed to prescription opioid pain medications such as hydrocodone, and oxycodone.

Variations in Signs and Symptoms

Except for methadone and buprenorphine, relatively no attention has been given to how the occurrence of specific signs and symptoms of NAS may differ as a function of a specific opioid. NAS assessment tools are based on the assumption that although there may be some individual variability, the signs and symptoms of opioid withdrawal are consistent. However, there are interesting data on differences between methadone and buprenorphine. Comparing the NAS profile before treatment or in the absence of treatment in infants exposed to methadone or buprenorphine under rigorous blinded conditions, the incidence of nasal stuffiness, sneezing, and loose stools was greater in the buprenorphine-exposed infants than in the methadone-exposed infants ($P < 0.02$), and no signs were more frequently observed in the methadone-exposed infants (Gaalema et al., 2012). Further, compared with the buprenorphine-exposed group, higher mean scores were found in the methadone-exposed infants for hyperactive Moro, disturbed and undisturbed tremors, failure to thrive, and excessive irritability ($P < 0.04$). These findings shed light on reported differences in NAS incidence, severity, and length of treatment duration between methadone and buprenorphine (Jones et al., 2010b; Meyer et al., 2015). These findings also point to the need for current assessment tools to be re-examined in terms of the way items are weighted and to determine the discriminant validity of the numerous items (Jones and Fielder, 2015).

Factors That Exacerbate NAS

Recently, in the absence of other risk factors, the use of prescription opioids during pregnancy has been found to be associated with a low absolute risk of NAS (absolute risk of 5.9 per 1000); in contrast, long-term opioid use (defined as >30 d) during pregnancy resulted in absolute risk of NAS of 220 per 1000 (Desai et al., 2015). This finding may provide some reassurance to women taking opioids for a limited time during pregnancy. The absolute risk of NAS associated with opioid use increases with such factors as longer history of opioid use, alcohol or other drug misuse, late pregnancy exposure to other psychotropic medications, and smoking (Desai et al., 2015).

How the interaction of nonopioids and opioids may impact the occurrence of NAS has not been well studied. However, existing literature suggests that this is an area that has implications for both clinical protocols and public policy. Marijuana, methamphetamines, and cocaine have not been found to produce a withdrawal syndrome, although cocaine, in combination with heroin (Fulroth et al., 1989), seems to exacerbate the opioid withdrawal. A review by Kocherlakota (2014) suggested that maternal use of cocaine and methadone may worsen withdrawal, but this is inconsistent with findings that infants born to mothers maintained on methadone who concomitantly used cocaine had significantly higher first withdrawal scores, but did not require higher doses of medication or required a longer duration of treatment than infants born to women maintained on methadone who did not use cocaine (Mayes and Carroll, 1996).

An early study identified alcohol as producing signs similar to opioid withdrawal in infants with fetal alcohol syndrome (Pierog et al., 1977), although the current CDC Fact Sheet (CDC, 2015) on Fetal Alcohol Spectrum Disorders does not list withdrawal as an associated perinatal problem. The general consensus is that although withdrawal symptoms may occur, the infant usually does not require treatment. Maternal use of alcohol and opioids in combination has also not been found to be associated with longer treatment of NAS due to prenatal methadone exposure (Seligman et al., 2008), but the number of women reporting alcohol use was minimal and there was no information regarding use patterns.

The substances that have consistently been found to contribute to the presentation of NAS are prescribed medications of SSRIs, and benzodiazepines and nicotine. When SSRIs are taken by opioid-dependent women receiving either methadone or buprenorphine, there is indication that SSRIs are related to both the presentation and treatment of NAS. Maternal use of SSRIs predicted higher peak NAS scores and higher doses of medication for infants requiring treatment for NAS in a sample of infants whose mothers had been randomly assigned to methadone or buprenorphine (Kaltenbach et al., 2012). However, use of SSRIs did not predict whether infants would require treatment. (Note: benzodiazepine use was an exclusion criterion of this study.) The results of this study are consistent with findings that infants prenatally exposed to both methadone and SSRIs were not more likely to be treated for NAS, but when they were treated, they required higher doses of medication (Jansson et al., 2010). Results are also consistent with several studies that found SSRIs did not predict length of treatment for infants prenatally exposed to methadone (Seligman et al., 2008; Dryden et al., 2009), and methadone and buprenorphine (Wachman et al., 2011).

Concomitant use of benzodiazepines and opioids may have adverse maternal consequences such as overdose sedation and possible death, and it also has consequences for infants undergoing NAS. A number of studies have found concomitant use of benzodiazepines in pregnant women receiving methadone or buprenorphine for opioid use disorders to be related to prolonged length of stay in infants requiring treatment for NAS (Seligman et al., 2008; Wachman et al., 2011; Pritham et al., 2012). This is a complex and difficult issue to address in that benzodiazepine use and misuse are prevalent among opioid-dependent pregnant women, are associated with illicit drug use, and intervention efforts require intensive approaches such as behavioral contracts, cognitive behavioral therapy, and medically monitored tapers (Hand et al., 2015).

Cigarette smoking in opioid-dependent women has also been found to adversely affect NAS, including total amount of medication required to treat NAS and length of treatment (Jones et al., 2013). The impact of smoking is related to the number of cigarettes smoked daily, emphasizing the importance of including smoking cessation/reduction-intervention programs in substance use disorder treatment for pregnant women.

TREATMENT

Screening and Assessment

Notably, assessment, which determines NAS severity, has received more attention than NAS screening, which determines the presence or absence of NAS. Emerging NAS in the 1970s resulted in assessment tools for evaluating infant withdrawal and determining the need for pharmacological treatment. The first and the most widely used is the Neonatal Abstinence Scoring Tool developed by Finnegan et al. (Finnegan et al., 1975; Sarkar and Donn, 2006). Other assessments include the Neonatal Drug Withdrawal Scale (Lipsitz, 1975); the Neonatal Narcotic Withdrawal Index (Green and Suffet, 1981); the Neonatal Withdrawal Inventory (Zahorodny et al., 1998), and the Withdrawal Assessment Tool (Franck et al., 2008). Of these 4, the first 3 are not represented in the current literature, and the Withdrawal Assessment Tool (WAT-1) has limited use as it is designed to assess opioid and benzodiazepine withdrawal.

The Neonatal Abstinence Scoring Tool, commonly referred to as the Finnegan score, consists of 21 items with 31 possible scores. Items are grouped into 3 categories of central nervous system disturbances, metabolic, vasomotor and respiratory disturbances, and gastrointestinal disturbances. Items associated with the greatest negative outcomes have the highest score. Assessment is conducted every 4 hours with treatment initiated with scores of 8 or greater on 3 consecutive assessments, or 12 or greater on 2 consecutive assessments.

Commonly, a ''modified'' Finnegan is noted, implying that the original tool has been changed. However, subsequent publications of the tool by Finnegan have never identified any modifications to the score. There was a format change in 1979 in the score sheet, that is, items group into the 3 categories mentioned above rather than listed line-by-line and some minor changes to 4 items (NIDA, 1979). No acknowledgment or discussion regarding these changes was included, and all subsequent publications use this form.

Although the Finnegan tool is widely used, there is concern that it is a subjective measure and that its original development was based on clinical judgments rather than a psychometric approach. In terms of clinical use, the most important element is using operational definitions for items and maintaining high interobserver reliability. Acceptable interobserver reliability is defined as agreement on 90% of the scored items (D'Apolito and Finnegan, 2010). This is essential to have confidence in the assessment and the course of treatment.

Distinct from most other NAS assessments, the Finnegan score also includes suggestions for dosing/weaning when pharmacological treatment is necessary. However, the most recent publication was in 1992 (Finnegan and Kaltenbach, 1992) and does not reflect the latest American Academy of Pediatrics (AAP) recommendations.

There have been several publications by other authors who have made modifications to the Finnegan score as part of clinical research projects. The most widely used modified tool is the MOTHER NAS Scale utilized in the Maternal Opioid Treatment Human Experimental Research (MOTHER) randomized controlled trial (RCT) (Jones et al., 2010b). It eliminated a number of items, for example, myoclonic jerks, mottling, nasal flaring, watery stools, and added 2 items, that is, irritability and failure to thrive. In addition to the MOTHER study, it is the standard instrument used in a number of clinical trials (Kraft and van den Anker, 2012). The MOTHER NAS Scale also includes a symptom rather than weight-based treatment regimen utilizing morphine sulfate (Jones et al., 2010b).

However, a brief screening tool that is a 3-item index (hyperactive Moro reflex, mild tremors when undisturbed, and increased muscle tone) produced an extremely useful discriminative index. Before conducting a full assessment, this tool can be easily, cheaply, and routinely administered, and may provide critical information regarding early identification of NAS (Jones et al., 2010a).

Nonpharmacological Approaches

Historically, comforting techniques such as swaddling, the use of a pacifier, and caring for the neonate in a quiet, dimly lit environment have been recommended for improving the management of NAS. However, none of these have been systematically evaluated to determine if they reduce the severity of NAS and the length of treatment. A more recent challenge to focus on the treatment of both mother and infant as an interactional dyad (Velez and Jansson, 2008) has led to a much broader contextual approach that suggests a number of related factors that may minimize NAS. It is also known that adoption of a systematic weaning protocol can result in shorter duration of opioid treatment and length of inpatient stay. Such adherence to a weaning protocol can also result in a lower rate of adjunctive therapy (Hall et al., 2014). Thus, organizational issues such as hospital practices make an important contribution to worsening or reducing NAS severity.

Breastfeeding seems to decrease NAS scores, the need for treatment, length of pharmacologic therapy, and length of hospital stay in infants prenatally exposed to methadone or buprenorphine (Abdel-Latif et al., 2006; Pritham et al., 2012; Wachman et al., 2013; Welle-Strand et al., 2013.). It has been well established that very little methadone or buprenorphine is present in breast milk, leading to guidelines by several medical academies/societies that women maintained on methadone or buprenorphine who are not using illicit drugs and who are engaged in treatment be encouraged and supported in breastfeeding (Academy of Breastfeeding Medicine, 2009; American Society of Addiction Medicine, 2012; World Health Organization, 2014). The impact of breastfeeding on NAS is not considered to be a function of breast milk per se, but rather the act of breastfeeding. The benefits of skin-to-skin contact and the soothing aspect of breastfeeding may help ameliorate some of the symptoms of NAS (Gray et al., 2002). Recommendations for breastfeeding in mothers who use chronic opioids for pain should include a safety evaluation, including type of medication, length of time on medication, and rapid increases in dose (Sachs, 2013).

Focus on the mother–infant dyad has also led to employing a rooming-in approach in which the mother cares for the infant and assists in the assessment of NAS symptoms.

Retrospective data from a Canadian program suggest that such an approach may be effective in reducing the need for NAS treatment and length of hospital stay (Abrahams et al., 2010). The Vermont Oxford Network (VON), a collaboration of health care providers whose mission is to improve the quality and safety of medical care for newborns, has undertaken a 3-year project, from 2013 to 2015, on improving the care of infants affected by NAS (Vermont Oxford Network, 2013–2015). Although they utilize a quality improvement approach rather than prospective research design, a number of hospitals have found that by integrating mothers as partners in the care of their infants, they have dramatically decreased the need to treat NAS and reduced length of hospital stay. Although these findings need to be replicated, they suggest that NAS maybe exacerbated by our current treatment approaches.

Pharmacological Approaches

Currently, 2 medications—oral morphine solution and methadone—are recommended by the AAP for treatment of NAS (Hudak and Tan, 2012). Tincture of opium is no longer recommended due to a high alcohol content and the risk of medication errors/overdose related to the high concentration of morphine (Hudak and Tan, 2012). A recent survey of neonatal intensive care units (NICUs) in the United States found that 80% used morphine and 18% used methadone (Vermont Oxford Network, 2013). However, available efficacy evidence for either medication from controlled trials is extremely limited and has been shown to have shortcomings under some dosing and weaning regimens (Gordon et al., 2012). Because of the short half-life of morphine, it is recommended that doses be administered no longer than 4 hours apart. However, the 2012 AAP report did not identify a specific dose and there is no generally accepted maximum dose (Kraft and van den Anker, 2012). Although there have been some data available suggesting that the refinement of a standard methadone weaning protocol using pharmacokinetic modeling was associated with a shorter duration of weaning and reduced length of hospital stay (Hall et al., 2015), more data are needed to guide its use in neonates (Wiles et al., 2015). The long half-life of methadone supports a long dosing interval, in which infants are often discharged before weaning. Infants discharged home on methadone usually have shorter hospitalizations, but longer duration of therapy (Backes et al., 2012).

Although not yet used in clinical practice, recent attention has focused on the use of buprenorphine for the treatment of NAS. Two open-label studies have reported promising findings of shorter length of treatment and length of hospital stay in infants randomized to buprenorphine compared with infants randomized to morphine for treatment of NAS (Kraft et al., 2008; Kraft et al., 2011). There are currently 4 active NCTs examining buprenorphine, including 1 double-blind, double-dummy RCT and 2 for treatment of NAS due to opioid and benzodiazepine exposure (eg, 5RO1DA029076; 5RO1DA031689; 2U54HD047905; 5R21HD081271).

Phenobarbital and clonidine have been established as effective adjunct therapy to morphine and methadone when maximum dose has been reached or when weaning is unsuccessful (Kocherlakota, 2014). Anecdotally, pentobarbital seems to be the most effective in infants with polydrug exposure, but concerns about its potential for harmful neurodevelopmental effects remain (Kraft and van den Anker, 2012).

Clonidine has also been found to be useful as an adjunct therapy to morphine (diluted tincture of opium [DTO]) in a RCT (Agthe et al., 2009). A prospective, nonblinded clinical trial, comparing the efficacy of clonidine versus phenobarbital as an adjunct medication to morphine sulphate, found that phenobarbital had clinically no significant shorter hospital stay, but significantly longer overall time on mediation compared with clonidine. Infants receiving clonidine were weaned from morphine and clonidine before discharge, whereas infants receiving phenobarbital were weaned from morphine, but discharged on phenobarbital to be weaned in an outpatient setting by the provider pediatrician. After discharge, phenobarbital was continued for an average of 3.8 months, with a range of 1 to 8 months (Surran et al., 2013). Although the length of hospital stay may be longer with the use of clonidine as an adjunct medication, there is less concern about long-term neurodevelopmental effects, and clonidine may be more effective than phenobarbital in reducing the gastrointestinal symptoms of NAS (Wiles et al., 2014).

Although there are no data available at this time to support the use of clonidine as first-line agent, there is a federally funded double-blind clinical trial currently investigating the use of morphine versus clonidine as a first-line medication for NAS (NCT01734551).

Treatment Protocols

Although the 2012 AAP guidelines recommend that every nursery should have a standardized protocol for the assessment and treatment of infants at risk and/or showing signs of withdrawal, a survey of accredited US neonatology fellowship programs found that only 55% had implemented a written protocol and only 69% used a published abstinence scoring system, of which 65% used the Finnegan score (Sarkar and Donn, 2006). Aggregate data across several surveys suggest significant variability in both diagnosis and treatment protocols (Kraft and van den Anker, 2012).

The value of using a standard treatment protocol has been highlighted by 2 recent publications. In a quality-improvement project that focused on high inter-rater reliability in NAS assessment and the implementation of a standard initiation and weaning protocol, length of stay was reduced by 50% (Asti et al., 2015). Similarly, a multicenter study that compared outcomes of infants managed with a standard NAS treatment and weaning protocol to infants managed without a standard protocol found that regardless of medication used for treatment, that is, morphine or methadone, infants managed with a standard protocol had shorter duration of treatment and shorter hospital stay (Hall et al., 2014).

The type of medication dose regimens may also vary. The traditional regimen is a weight-based approach, that is, the individual dose was determined according to the infant's weight. However, recently, some institutions and research protocols use a symptom-based approach in which the dose is based on the severity of the infant's symptoms (Kraft and van den Anker, 2012). To date, there are no systematic studies that have evaluated these 2 therapeutic regimens.

FUTURE DIRECTIONS

As noted in the ''Introduction'' section, the rise in opioid use and misuse has produced an unprecedented focus on NAS from both the political-judicial sphere and the medical community. Accordingly, there are 4 areas on which future research should focus to guide both medical care and public policy. First, prospective studies that identify the best ways to support mothers and children are needed. For example, effective ways for engaging mothers in treatment and identifying interventions that improve rates of mothers maintaining custody may help prevent maternal substance use relapse and improve child outcomes. Second, mechanisms need to be identified that promote communication/education between government and judicial officials and the medical community so that legislation and judicial actions are not punitive and harmful to mothers and their children. Third, hospital policies regarding urine and other biological matrices testing in mothers and infants for substance use or exposure need to be critically examined as to the benefits or harmful ramifications to mother and child. Fourth, assessment and treatment of NAS must be re-examined. An objective measure of neonatal opioid withdrawal derived from a rigorous psychometric approach is needed in addition to research that focuses on evaluation of pharmacologic and nonpharmacological treatment protocols to determine which ones are the most supportive of mother and child, and effective in alleviating NAS. In conclusion, it is time for the media, political-judicial spheres, and the medical community to move beyond emotional reaction and take a rationale response to NAS. NAS occurrence and treatment must be viewed in the larger context in which it occurs and seen as only one of the many components of maternal and child health and well-being.

REFERENCES

Abdel-Latif ME, Piner J, Clews S, et al. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug dependent mothers. *Pediatrics* 2006;117(6):e1163–e1169.

Abrahams RR, Mackay-Dunn MH, Nevmerjitskaia V, et al. An evaluation of rooming-in among substance-exposed newborns in British Columbia. *J Obstet Gynaecol Can* 2010;32:866–871.

Academy of Breastfeeding Medicine. ABM Clinical Protocol #21. Guidelines for breastfeeding and the drug dependent woman. *Breastfeed Med* 2009;4(4):225–228.

American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women; American Society of Addiction Medicine. ACOG Committee No 524. Opioid abuse, dependence and addiction in pregnancy. *Obstet Gynecol* 2012;119:1070–1076.

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):e849–e856.

American Society of Anesthesiology. Practice guidelines for chronic pain management. *Anesthesiology* 1997;6:995–1004.

Asti L, Magers JS, Keels E. A quality improvement project to reduce length of stay for neonatal abstinence syndrome. *Pediatrics* 2015;135:e495.

Backes CH, Backes CR, Gardner D, et al. Transitioning methadone treated infants from an inpatient to an outpatient setting. *J Perinatol* 2012;36(6):425–430.

Blinick G, Wallach RC, Jerez E. Pregnancy in narcotic addicts treated by medical withdrawal. The methadone detoxification program. *Am J Obstet Gynecol* 1969;105:997–1003.

Blinick G, Wallach RC, Jerez E, et al. Drug addiction in pregnancy and the neonate. *Am J Obstet Gynecol* 1976;125:135–142.

CDC Fact Sheet on Fetal alcohol Spectrum Disorders. Available at: www.cdc.gov/ncbdd/fasd/documents. Accessed October 14, 2015.

Creanga AA, Sabel JC, Ko JY, et al. Maternal drug use and its effect on neonates: a population-based study in Washington state. *Obstet Gynecol* 2012;119(5):924–933.

D'Apolito K, Finnegan L. Assessing Signs and Symptoms of Neonatal Abstinence using the Finnegan Scoring Tool: An Inter-Observer reliability Program. Neo Advances LLC; 2010. Available at: neoadvances.com. Accessed October 12, 2015.

Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: a population based cohort study. *BMJ* 2015;350:h2102.

Desmond MM, Schwanecke RP, Wilson GS, et al. Maternal barbiturate utilization and neonatal withdrawal symptomatology. *J Pediatr* 1972;80(2):190–197.

Dryden C, Young D, Hepburn M, et al. Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *Br J Obstet Gynecol* 2009;116(5):665–671.

Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman RA, Friedman SB, Nelson NM, et al., eds. Primary Pediatric Care. 2nd ed. St. Louis, MO: Mosby; 1992:1367–1378.

Finnegan LP, Connaughton JF, Kron RE, et al. Neonatal abstinence syndrome: assessment and management. *Addict Dis* 1975;2:141–158.

Franck LS, Harris SK, Soetenga DJ, et al. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med* 2008;9:573–580.

Fulroth R, Phillips B, Durand DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am J Diseases Child* 1989;113(6):714–715.

Gaalema DE, Scott TL, Heil SH, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone-versus buprenorphine-exposed infants. *Addiction* 2012;107(Suppl 1):53–62.

Gaalema DE, Heil SH, Badger GJ, et al. 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.

Gordon AL, Lopatko OV, Haslam RR, et al. Ineffective morphine treatment regimen for the control of Neonatal Abstinence Syndrome in buprenorphine and methadone exposed infants. *J Dev Orig Health Dis* 2012;3(4):262–270.

Gray L, Miller LW, Philipp BL. Breastfeeding is analgesic in healthy newborns. *Pediatrics* 2002;109:590–593.

Green M, Suffet F. The Neonatal Narcotic Withdrawal Index: a device for the improvement of care in the abstinence syndrome. *Am J Drug Alcohol Abuse* 1981;8:203–213.

Hall ES, Wexelblatt SL, Crowley M, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics* 2014;134(2):e527–e534.

Hall ES, Wexelblatt SL, Crowley M. Implementation of a neonatal abstinence syndrome scoring weaning protocol. *Pediatrics* 2015;136(4):e803–e810.

Hand, DJ, Short VL, Abatemarco DJ, et al. Illicit drug use across pregnancy among benzodiazepine-using and non-using methadone maintained women. Presented at the Vermont Center on Behavior and Health. 3rd Annual Conference on Behavior Change, Health, and Health Disparities, Oct. 1, 2015, Burlington, VT.

Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129: e540–e560.

Jansson LM, Dipietro JA, Elko A, et al. Infant autonomic functioning and neonatal abstinence. *Drug Alcohol Depend* 2010;109:198–204.

Jones HE, Fielder A. Neonatal abstinence syndrome: historical perspective, current focus, future directions. *Prevent Med* 2015;80:12–17.

Jones HE, Velez ML, McCaul ME, et al. Special treatment issues for women. In: Strain EC, Stizer M, editors. Methadone Treatment for Opioid Dependence. Baltimore, MD: Johns Hopkins University Press; 1999. p. 251–280.

Jones HE, Harrow C, O'Grady KE, et al. Neonatal abstinence scores in opioid-exposed neonates: a blinded comparison. *J Opioid Manag* 2010;6:409–413.

Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363:2320–2331.

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.

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.

Kieviet N, Dolman KM, Honig A. The use of psychotropic medication during pregnancy: how about the newborn? *Neuropsychiatr Dis Treat* 2013;9:1257–1266.

Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics* 2014;134:e547–e561.

Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. *Pediatr Clin North Am* 2012;59:1147–1165.

Kraft WK, Gibson E, Dysart K, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. *Pediatrics* 2008;122(3):e601–e607.

Kraft WK, Dysart K, Greenspan JS, et al. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid syndrome. *Addiction* 2011;106(3):574–580.

Lind JN, Peterson EE, Lederer PA, et al. Infant and maternal characteristics in neonatal abstinence syndrome: selected hospitals in Florida, 2010–2011. *MMWR Surveill Sumn* 2015;64(08):213–216.

Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. Pragmatic evaluation of its efficacy. *Clin Pediatr (Phila)* 1975;14(6):592–594.

Mayes LC, Carroll KM. Neonatal withdrawal syndrome in infants exposed to cocaine and methadone. *Subst Use Misuse* 1996;31(2):241–253.

Meyer MC, Johnston AM, Crocker AM, et al. Methadone and buprenorphine for opioid dependence during pregnancy: a retrospective cohort study. *J Addict Med* 2015;9(2):81–86.

National Institute of Drug Abuse. Drug Dependence in Pregnancy: Clinical Management of Mother and Child. DHEW Publication No (ADM) 79-678, 1979.

Patrick SW, Schumacher RE, Benneyworth BD, et al. Neonatal abstinence syndrome and associated health care expenditures: United States 2000–2009. *JAMA* 2012;307:1934–1940.

Pierog S, Chandavasu O, Wexler I. Withdrawal symptoms in infants with the fetal alcohol syndrome. *J Pediatr* 1977;90(4):630–633.

Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *J Obstet Gynecol Neonatal Nurs* 2012;41(20):180–190.

Rementeria JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. *J Pediatr* 1977;90(1):123–126.

Sachs HC, American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk. *Pediatrics* 2013;132:e796–e809.

SAMHSA. Medication assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 08-4214. Rockville, MD: Substance Abuse Mental Health Service Administration; 2005.

SAMHSA Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No (SMA) 13-4795. Rockville, MD: Substance Abuse Mental Health Services Administration; 2013.

Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national study. *J Perinatol* 2006;26(1):15–17.

Seligman NS, Salva N, Hayes EJ, et al. Predicting length of treatment for neonatal abstinence syndrome in methadone exposed neonates. *Am J Obstet Gynecol* 2008;199. 396.e1-396.e7.

Surran B, Visintainer P, Chamberlain S, et al. Efficacy of clonidine versus phenorbarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome; a prospective randomized clinical trial. *J Perinatol* 2013;33:954–959.

Terplan M, Kennedy-Hendricks A, Chisolm M. Prenatal substance use: exploring assumptions of maternal unfitness. *Subst Abuse* 2015;9(s2):1–4.

Velez M, Jansson LM. The opioid dependent mother and newborn dyad: non-pharmacologic care. *J Addict Med* 2008;2(3):113–120.

Vermont Oxford Network. 2013. iNICQ 2013: Controversies in the Care of Infants and Families Affected by Neonatal Abstinence Syndrome. Available at: www.public.vtoxford.org. Accessed October 12, 2015.

Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence. *J Addict Med* 2011;5(4):293–299.

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;309910:1821–1827.

Warren MD, Miller AM, Taylor J, et al. Implementation of a statewide surveillance system for neonatal abstinence syndrome-Tennessee 2013. *MMWR Surveill Sumn* 2015;64(05):125–128.

Welle-Strand GK, Skurtveit S, Jansson LM, et al. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *Acta Paediatr* 2013;102(11):1060–1066.

Wiles JR, Iseman BI, Ward LD, et al. Current management of neonatal abstinence syndrome secondary to in-utero opioid exposure. *J Pediatr* 2014;165(3):440–446.

Wiles JR, Iseman B, Mizuno T, et al. Pharmacokinetics of oral methadone in the treatment of neonatal abstinence syndrome: a pilot study. *J Pediatr* 2015;167(6):1214–1220.

World Health Organization. Guidelines for the Identification and Management if Substance Use and Abuse Disorders in Pregnancy. Geneva, Switzerland: World Health Organization; 2014.

Zahorodny W, Rom C, Whitney W, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *J Dev Behav Pediatr* 1998;19:89–93.

Zelson C, Rubio E, Wasserman E. Neonatal narcotic addiction: 10 year observation. *Pediatr* 1971;48:178–189.

