Published in final edited form as:
J Pediatr. 2014 September ; 165(3): 440–446. doi:10.1016/j.jpeds.2014.05.010.

Current Management of Neonatal Abstinence Syndrome Secondary to Intrauterine Opioid Exposure

Jason R Wiles, MD[1], **Barbara Isemann, RPh**[2], **Laura P Ward, MD**[1,4], **Alexander A Vinks, PharmD, PhD**[3,4], and **Henry Akinbi, MD**[1,4]

[1]Perinatal Institute, Division of Neonatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[2]Department of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH, USA

[3]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[4]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Keywords

Illicit drug; Infant; NAS; Neonatal Abstinence Syndrome; Neonatal Withdrawal; Neonate; Opioid; Opiate; Pregnancy; Withdrawal

Neonatal abstinence syndrome (NAS) comprises a constellation of drug withdrawal symptoms that result from chronic intrauterine exposure to a variety of substances, including opioids, benzodiazepines, barbiturates, selective serotonin reuptake inhibitors, ethanol, nicotine and caffeine. Most non-opioid fetal drug exposures result in limited clinical presentation, respond well to supportive care measures and rarely require pharmacologic intervention [1, 2]. Chronic *in utero* exposure to opioids is well characterized and is particularly problematic because of its high prevalence and frequent need for pharmacotherapy to mitigate withdrawal signs, especially when the opioid exposure is in the broader context of maternal polysubstance consumption.

Epidemiology of Neonatal Abstinence Syndrome

In a recent national survey, 18.3% of pregnant teens, 9% of pregnant women aged 18-25 years and 5.9% of all pregnant women reported some illicit drug use [3]. Opioids specifically are ubiquitous and the upsurge in use is contemporaneous with pain management standards set by the Joint Commission on Accreditation of Healthcare

Corresponding Author: Henry Akinbi, M.D., Cincinnati Children's Hospital Medical Center, Division of Neonatology, 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229-3039, henry.akinbi@cchmc.org, Phone: (513) 636-8918, Fax: (513) 636-7868.

The authors declare no conflicts of interest.

Organizations in 2001. Correspondingly, there has been a 5-fold increase in opioid use during pregnancy over the last decade with a prevalence of 5.6 per 1000 hospital births [4-7]. The state of Ohio recently reported a 5-fold increase in the frequency of maternal drug abuse and dependency diagnoses at the time of delivery that were related to opioids, placing it second only to marijuana, and a 6-fold increase in hospitalizations due to NAS (from 1.4 to 8.8 per 1000 live births) in less than a decade [8]. The incidence of NAS has also tripled nationally, affecting 47-57% of infants born to mothers on methadone or buprenorphine maintenance therapy [7, 9]. The economic burden posed by these trends is staggering, with average hospital inpatient cost as high as $59,500 per hospital birth for infants with NAS [8]. In 2011, the treatment of NAS was associated with over $70 million in charges in the state of Ohio alone. Medicaid was the primary payer source for 85% of NAS discharges over the same timeframe which is significantly higher than the percentage of all Ohio births billed to Medicaid (55%) [8].

Clinical Presentation of NAS

NAS manifestations are modulated by a combination of maternal and neonatal factors, including the opioid dose, frequency and timing prior to delivery, maternal pharmacokinetics (PK), placental metabolism, concurrent medications and neonatal PK and pharmacogenomics. The clinical presentation of NAS reflects higher abundance of opioid receptors in the nervous system and the gastrointestinal tract. These may exhibit as neurologic excitability (e.g. tremors, irritability, increased muscle tone, frequent yawning or sneezing, seizures), gastrointestinal dysfunction (e.g. feeding difficulty, uncoordinated sucking, vomiting, diarrhea, poor weight gain), and autonomic signs (e.g. diaphoresis, nasal stuffiness, fever, mottling, temperature instability). Other signs include respiratory distress and skin excoriation. The exact mechanism implicated in signs of NAS remains unclear though it may result from increased adenylyl cyclase activity and norepinephrine release upon cessation of mu-opioid stimulation after birth [10].

In the absence of evidence to substantiate alternate diagnoses, a careful maternal history of alcohol, tobacco, prescription and nonprescription drug use should be ascertained using one of several tools including the popular 4Ps Plus (Parents, Partner, Past, Pregnancy) [11]. Risk factors associated with maternal substance abuse include lack of prenatal care, premature delivery, sexually transmitted infections such as hepatitis C virus and human immunodeficiency virus, cigarette smoking, fetal intrauterine growth restriction and poor maternal nutritional status [12]. In contrast, the risk of developing NAS is reduced by the lack of polysubstance exposure, prematurity, and minor alleles in the mu-opioid receptor (*OPRM1*) and catechol-O-methyltransferase (*COMT*) genes [13, 14].

Clinical suspicion of intrauterine opioid exposure may be corroborated using toxicology screening adapted for urine, meconium, hair follicle or umbilical cord tissue [15]. Umbilical cord analysis may be advantageous because of comparative ease in obtaining samples, relatively rapid availability of testing results (slower than urine but faster than meconium) and results that are comparable with meconium analysis [16]. In many cases, a positive opioid screen will trigger confirmatory testing that can distinguish the specific drug of exposure (e.g. heroin from fentanyl). These additional results may be helpful clinically to

determine the source of drug exposure and ultimate risk for withdrawal (e.g. a screen positive for fentanyl is likely related to medication received during labor and holds no risk for withdrawal from short delivery exposures). Also, clinicians should know the opioids for which the test they are ordering screen, as it may not identify the presence of all drugs of abuse (e.g. buprenorphine or methadone might not be included in the screen). Clinicians should order toxicology screens that will detect common opioid exposures in their patient population.

Hospital charges for urine, meconium and umbilical cord tissue toxicology screening are relatively comparable costing $300-550, $250-500 and $400-800 respectively. It should be noted, however, that charges vary between institutions depending on the total number of drugs screened, where the analysis is performed (e.g. in-house versus third party service vendor) and additional charges incurred for confirmation testing. Recent developments in high-end tandem mass spectrometry techniques hold promise for both identification and quantification of drugs and active metabolites. Local availability of such technology at competitive prices is possible and could expedite meconium toxicology screens, thereby contributing to utility in medical decision-making.

Assessment Tools for NAS

The Neonatal Intensive Care Unit Network Neurobehavioral Scale was developed for use in the neonatal intensive care unit to better understand the long-term implications of intrauterine exposure to opioids [17]. Although the complexity of this comprehensive and sensitive research tool makes its routine use for clinical purposes impractical, it shows that opioid-exposed infants demonstrate high levels of dysregulated behavior and stress, is predictive of worse neurodevelopmental outcome and may be useful in identifying behavioral dysfunction that is amenable to early intervention [17-19]. Limited available data suggest that infants exposed to methadone are more likely to have a lower IQ, exhibit attention deficit hyperactivity disorder and receive other disruptive behavior diagnoses. However, these findings should be interpreted with caution because of confounding variables such as environmental, genetic and socioeconomic factors. More studies will be needed to delineate the risk associated with exposure to non-methadone opioids [20].

Infants at risk for NAS should be monitored diligently during the initial days after birth. Several standardized scoring systems have been developed to assist in identification, quantification of severity and assessment of response to treatment of term infants with NAS. These include the Finnegan Neonatal Abstinence Severity Score, Lipsitz tool, Neonatal Narcotic Withdrawal Index and Neonatal Withdrawal Inventory [21-24]. Though careful training of the staff utilizing these assessment tools can increase interrater reliability, scoring mechanisms remain substantially subjective. Additionally, the reduced capacity of preterm and ill infants with *in utero* opioid exposure to exhibit typical signs of withdrawal limits generalizability. For example, preterm infants may demonstrate less signs of withdrawal due to neurologic immaturity, whereas therapy administered to ill infants may impede full evaluation of withdrawal (e.g. intubation, sedation, NPO). Despite these shortcomings, the authors' practice aligns closely with recommendations from the American Academy of Pediatrics (AAP) which strongly encourages the use of protocols for evaluation and

management of newborn withdrawal and the utilization of standardized scoring systems with which the staff is comfortable [25]. Although standardization of treatment is known to enhance outcomes in many areas of medicine, to our knowledge there are no published NAS-specific data that demonstrate reduced length of stay or other clinically important outcome with the use of a protocol. However, the lack of such data should not preclude practitioners from exercising good clinical judgment and implementing sound evidence-based protocols.

Management of Infants at Risk for NAS

The risk of withdrawal is variable and is related to the type of opioid, dose and timing of exposure. The AAP recommends that infants exposed to shorter half-life drugs and who manifest no signs of withdrawal could be safely discharged after 3 days of observation whereas it is reasonable to monitor infants exposed to drugs with a longer half-life, such as methadone, for a longer period of time (4 to 7 days) [25]. The authors' institutional policy calls for universal maternal drug screening during parturition, a minimum 72-hour observation for shorter half-life drugs implicated in withdrawal and a minimum 96-hour observation for infants exposed to methadone or buprenorphine *in utero*.

The paucity of evidence to support any single treatment strategy has resulted in active debate as to the most effective management strategy. This is at least partially due to the absence of data on long-term outcome to compare infants who have *in utero* opioid exposure without withdrawal with those who develop signs of withdrawal only requiring non-pharmacologic management and to those who ultimately develop symptoms severe enough to merit pharmacologic treatment. However, every nursery should adopt a standardized protocol for assessing and managing infants at risk for NAS including a specified minimum duration of observation. The staff should be trained in administering the assessment tool selected by the nursery.

Non-Pharmacologic Treatment of NAS

Mothers participating in opioid treatment programs should be encouraged to breastfeed their infants; active or recent illicit drug use is considered a contraindication to breastfeeding [26, 27]. Breastfeeding has been associated with less severe symptoms of NAS and a reduced requirement for pharmacologic intervention [28, 29]. In a recent study by Welle-Strand et al, this effect was found to be particularly prominent in a cohort of mother-infant dyads where the mothers received methadone maintenance treatment for opioid dependency. They reported that breastfed neonates with intrauterine exposure to methadone had a significantly lower incidence of pharmacologically-treated NAS (53 vs 80%) [30]. However, healthcare providers should be aware that postpartum women who are in opioid maintenance programs have high breastfeeding cessation rates which may place infants at risk of developing withdrawal symptoms after abrupt discontinuation of breastfeeding despite relatively low concentrations of methadone in breast milk [29, 30]. In the absence of human milk, frequent feedings with high caloric density formula may be needed to optimize growth.

The initial management of all infants suspected of having or at risk for developing NAS should center on non-pharmacologic interventions as this may mitigate the need for

medication. An individualized non-pharmacologic treatment strategy developed by the healthcare team based on signs and behaviors to support the infant's autonomic, sensory, motor and interactive development should aide in the optimization of patient care [31]. Environmental conditions that minimize external stimuli such as nursing in quiet, dimly-lit places and coordinating interventions to allow more quiet time should be encouraged. Gentle handling and positioning may be used to maximize containment, minimize auto-stimulation and facilitate self-regulation (e.g. swaddling with blanket rolls, offering non-nutritive sucking). Rocking or swaying to increase the infant's comfort has been suggested, although rocking is not tolerated by all infants [25, 32]. Frequent, small volume feeds are sometimes utilized to minimize hunger and address suboptimal intake. Increased caloric density feeds may be necessary to ensure adequate weight gain in the face of increased energy expenditures that may occur in addition to gastroesophageal reflux, emesis, and diarrhea. Involving parents through "rooming in" and providing active neonatal care should be encouraged whenever feasible. This allows for parental bonding, more consistent breastfeeding where appropriate and may decrease length of hospitalization [33, 34].

Pharmacologic Treatment of NAS

Several medications including paregoric, tincture of opium, phenobarbital, morphine, methadone, buprenorphine and clonidine have been employed to treat NAS. The AAP and Cochrane Reviews have concluded that opioids are ideal treatment for neonates exposed to opioids *in utero* [25, 35, 36]. The treatment of choice is less clear for NAS secondary to exposure to substances other than opioids because of paucity of data as it relates to medications used to treat NAS and their pharmacokinetics, pharmacodynamics (PD) and pharmacogenomics. Additionally, practitioners tend to favor monitoring for resolution of signs of NAS rather than targeting a predetermined maximum medication dose [37].

Morphine—Oral morphine is the most common first-line medication used in the treatment of NAS amongst nurseries in the United States [38]. Many neonatal intensive care units favor the use of this full mu-opioid receptor agonist for its short half-life (4 hours) and the ease of titrating the dose to clinical response. The PK and PD of intravenous morphine in neonates demonstrate substantial interpatient and intrapatient variability though such studies are lacking for oral formulations where variability is expected to be even larger [39, 40]. Reported initial starting doses for oral administration are highly variable but the AAP policy recommends 0.04 mg/kg/dose given every 3-4 hours [25, 41]. Down-titration of dosing generally occurs after 48 hours of clinical stabilization. Subsequently, the daily dose is often decreased by 10% until approximately 0.15 mg/kg/day is attained, after which the medication is discontinued [42]. It should be noted that there is no consensus or evidence-based maximum dose before starting adjunct therapy or minimum dose before medication discontinuation.

Methadone—Methadone is a synthetic, full mu-opioid agonist with a half-life of 25-32 hours. Its use could be advantageous compared with shorter acting medications by providing a more consistent serum concentration over time. Physiology-based PK modeling of oral methadone in infants predicts substantial interpatient variability, but this has yet to be validated [43]. One retrospective study comparing oral morphine with oral methadone

reported no difference in length of hospitalization [44]. Oral methadone is sometimes used to transition patients with NAS to outpatient care. This strategy is associated with a reduced length of hospitalization but results in a larger cumulative opioid exposure [45]. At the authors' institution, the starting dose for NAS is 0.05 mg/kg/dose every 6 hours though the dose may be increased to 0.1 mg/kg/dose if symptoms of NAS do not improve within 24 hours of starting the standard dosing strategy, a range consistent with the AAP policy statement [25, 29]. The dose and frequency are decreased after 24-48 hours of stable withdrawal scores. Methadone is often discontinued when signs of NAS remain abated at a dose of 0.01mg/kg dose every 24 hours. In a recent report, 60% of infants with NAS were unable to wean at 48 hours when the starting dose was 0.1 mg/kg/dose every 6 hours [46]. Due to the paucity of PK and PD data for methadone in neonates, it is difficult to make definitive conclusions regarding these findings; however, it highlights the urgent need for additional study to address presumed large inter-individual drug variability.

Buprenorphine—Buprenorphine is an effective maintenance therapeutic in the adult population as well as during pregnancy [9, 47]. Sublingual buprenorphine is also a treatment modality that is in the early stages of investigation for the treatment of NAS. It is a long-acting partial mu-opioid receptor agonist with limited neonatal PK data. The safety profile is enhanced by the agonist/antagonist properties of the drug that create a ceiling effect against respiratory depression. Limited reports on buprenorphine have been promising when compared with oral morphine in two open-label clinical trials [48, 49]. Its use was noted to result in shorter hospitalization and length of therapy as compared with oral morphine but is associated with increased need for adjunctive therapy. The reported starting dose was 15.9 μg/kg/day divided every 8 hours. When signs of NAS subsided, doses were decreased by 10% daily until the dose was 10% of the starting dose.

Several current clinical investigations listed on the registry (clinicaltrials.gov) may help optimize pharmacologic treatment strategies. These studies are examining the PK of oral methadone when used to treat NAS (NCT01754324), expanded use of sublingual buprenorphine for withdrawal secondary to *in utero* benzodiazepine and opioid exposure (NCT01671410) and the PK and utility of sublingual buprenorphine versus oral morphine in the treatment of NAS (NCT01452789). There are also masked trials comparing efficacy of morphine versus methadone (NCT01804075) and buprenorphine versus morphine (NCT01708707). As the PK and PD properties of these drugs are delineated in neonates, treatment protocols may be optimized and could result in evidence-based recommendations regarding first-line therapies.

Adjunctive Pharmacologic Therapies

Despite best efforts to maintain monotherapy regimens, adjunctive pharmacologic agents are often required for infants who fail to respond to first-line medications. Common indications for adjunctive therapy include poorly-controlled signs of withdrawal despite optimizing the dose of a first-line treatment agent, a persistent inability to wean first-line treatment doses, or relapse of signs of NAS after withdrawal has been adequately treated.

Phenobarbital

Phenobarbital is a $GABA_A$ receptor agonist with a long half-life in neonates (67-115 hours), which decreases substantially over the first several weeks of life. A recent Cochrane review concluded that phenobarbital used as a first-line agent is associated with a higher incidence of seizures and longer treatment duration than opioids [36]. Consequently, it should only be considered for second-line treatment or adjunctive therapy. Its sedative qualities and $GABA_A$ receptor activity in the central nervous system make it a preferred adjunct in infants exposed concomitantly to benzodiazepines. Dosing practices extend over a wide range for adjunctive phenobarbital. An oral loading dose of 20 mg/kg or 10mg/kg every 12 hours for two or three doses followed by 5-10 mg/kg/day of alcohol-free compounded phenobarbital has been reported [50]. Once instituted, the common practice is to discharge patients home on phenobarbital with a goal of allowing infants to outgrow the dose over time. Unfortunately, gaps in knowledge regarding the effects of phenobarbital exposure and pervasive concerns surrounding impaired long-term neurodevelopment will persist, as a registered study designed to address this question was recently terminated due to slow patient recruitment (NCT01089504).

Clonidine

An α_2-adrenergic receptor agonist used in the treatment of withdrawal in adults, clonidine is also used for adjunctive NAS therapy [51, 52]. A non-linear mixed effects model of the PK of oral clonidine suggested an optimal (mean) dose of 1.5 μg/kg/dose administered every four hours starting in the second week of life to accommodate increased clearance over the first month of life [53]. This strategy represents a 50% increase from the dose of 1 μg/kg/dose used in clinical trials and has not been validated. The AAP dosing recommends of 0.5-1 mcg/kg/dose given every 3-6 hours [25]. A recent study comparing clonidine versus phenobarbital as adjunctive treatment was terminated early in favor of phenobarbital [54]. However, clonidine had the advantage of being discontinued prior to discharge whereas patients on phenobarbital were often discharged home and maintained on the medication for several months. In addition, clonidine also presents less concern about long-term neurodevelopmental outcomes and may ameliorate gastrointestinal symptoms of NAS better than phenobarbital. Some experts have been encouraged by the potential of using this non-narcotic medication as a first-line agent in treating NAS. One double-blinded trial comparing morphine with clonidine may address the utility for this indication (NCT01734551).

Future Directions

Treatment of the maternal-infant dyad should be the goal. However, most facilities are not equipped to support the mother during the entire period of observation and infants are often admitted to an intensive care unit after pharmacologic treatment is initiated. Regardless of the hospital set up, few programs have the capability to adopt a more comprehensive model of care that includes sex-specific approaches to medical and mental health care, individual and group addiction treatment, advanced skills development around mothering, nutrition and regaining self-worth, and appropriate neonatal care. The success of community-based treatment facilities that have adopted this comprehensive program is laudable. Success rates

as high as 73% of mothers remaining drug-free (off all opioids) 3 months following completion of residential treatment has been achieved (personal communication, Jeane Cole, LSW, May 2013, unpublished data). Similar models have also been reported to be cost-effective [55].

Additionally, the study of opioid dependence is often confounded by a myriad of complex psychosocial issues. As noted by Jones et al, the efforts of future research should be focused on understanding the effects of medications used for both mother and child in the context of these additional risk factors such as psychiatric diseases, nicotine use, alcohol consumption, and use of other withdrawal-inducing legal or illicit exposures [56]. Developing strategies to reduce the initiation of opioid drug use is likewise important.

Efforts to improve or revamp current assessment tools may result in more reproducible measures of neonatal withdrawal and would be aided by the development of more objective measures of clinical status such as serum or genetic biomarkers. Attempts to identify the key pharmacogenetic markers that might explain variability in response to medications and more severe withdrawal are being investigated [14, 57, 58]. Rapid availability of quantitative drug and metabolite screening of likely exposures shows promise. PK interpretation may be added to develop an appropriate, individualized pharmacologic therapy. However, these technologies would have to be set up locally to ensure prompt turn-around of results and may not be feasible or cost-effective in all settings. Additional investigation regarding the utility of these technologies for the NAS population will be required before definitive recommendations could be made.

No long-term longitudinal outcome data assessing the effects of chronic *in utero* opioid exposure are currently available with regards to infants who have been treated for NAS. Certainly, this is a complex multi-factorial question that should be addressed. Some of the variables that may likely influence risk for poor developmental outcomes include the degree of intrauterine drug exposure, the extent of neonatal withdrawal, long-term effects of drugs used for the treatment of NAS, genetic predisposition, socio-economic factors, environmental influences and long-term access to medical care. Understanding the most influential factors determining long-term developmental outcomes should be a component of targeted, cost-effective and comprehensive treatment strategies.

The cost of various treatment strategies is an important consideration in all facets of medical practice. The cost of toxicology screening (urine, meconium or umbilical cord tissue) is similar for all three tests and is mostly driven by the total number of drugs screened, individual hospital contracts and the need for additional confirmation testing. The cost of medication used in the pharmacologic management of NAS has a minimal impact on the total cost of care. If one assumes the treatment of a 4-kilogram baby and starting doses suggested in this article, the average wholesale price for the first day of pharmacologic treatment of NAS is as follows: morphine ($0.07), methadone ($0.03), buprenorphine ($2.01), phenobarbital ($0.42) and clonidine ($0.03) [59]. Of course, this does not include pharmacy or nursing labor in dispensing or administering the products. Hospital charges undoubtedly vary between institutions and regions of the country but until better evidence to support a superior individual pharmacologic treatment strategy emerges, the authors suggest

that providers be cognizant of local data and tailor treatment protocols to the most cost-effective strategy. Backes et al have described perhaps the most creative and intriguing approach to cost containment which involves inpatient stabilization of NAS followed by outpatient management with oral methadone [45]. The efficiency of reduced total hospital days is very appealing but may not be suitable for all patients and should always be balanced against patient safety and the uncertain long-term effect of increased total opioid exposure.

In an era of medicine centered on cost containment and evidence-based treatment strategies, NAS presents many opportunities for quality improvement. The importance of well-designed drug studies in children and especially in neonates is being highlighted [60]. It is crucial that agents used in the pharmacologic treatment of NAS be more fully characterized in order to optimize treatment protocols. We can further ameliorate outcomes in infants with NAS by focusing treatment on the maternal-infant dyad, devising objective assessment tools, investigating potential biomarkers of disease, characterizing the role of genetic variability, devising thoughtful treatment protocols based on the best available evidence and designing sound longitudinal studies. Maintaining the status quo in NAS treatment vitiates progress. Further research in these areas is paramount to the development of cost-effective treatment and enhanced outcomes.

Acknowledgments

J.W. was supported by the National Institutes of Health (5T32HD069054).

References

1. O’Donnell M, Nassar N, Leonard H, Hagan R, Mathews R, Patterson Y, et al. Increasing prevalence of neonatal withdrawal syndrome: population study of maternal factors and child protection involvement. Pediatrics. 2009; 123:e614–e21. [PubMed: 19336352]
2. Wagner CL, Katikaneni LD, Cox TH, Ryan RM. The impact of prenatal drug exposure on the neonate. Obstet Gynecol Clin North Am. 1998; 25:169–94. [PubMed: 9547766]
3. SAMHSA (Substance Abuse and Mental Health Services Administration). 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 and Mental Health Services Administration; 2013.
4. Hayes MJ, Brown MS. Epidemic of prescription opiate abuse and neonatal abstinence. JAMA. 2012; 307:1974–5. [PubMed: 22546607]
5. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. Pharmacoepidem Dr S. 2008; 17:997–1005.
6. Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. Am J Obstet Gynecol. 2011; 204:259 e1–4. [PubMed: 21376165]
7. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. JAMA. 2012; 307:1934–40. [PubMed: 22546608]
8. Massatti, R.; Falb, M.; Yors, A.; Potts, L.; Beeghly, C.; Starr, S. Neonatal abstinence syndrome and drug use among pregnant women in Ohio: 2004-2011. Columbus, OH: Ohio Department of Mental Health and Addiction Services; 2013.
9. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010; 363:2320–31. [PubMed: 21142534]

10. Anand KJ, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics. 2010; 125:e1208–25. [PubMed: 20403936]
11. Chasnoff I, Wells A, McGourty R, Bailey L. Validation of the 4P's Plus© screen for substance use in pregnancy validation of the 4P's Plus. J Perinatol. 2007; 27:744–8. [PubMed: 17805340]
12. Keegan J, Parva M, Finnegan M, Gerson A, Belden M. Addiction in pregnancy. J Addict Dis. 2010; 29:175–91. [PubMed: 20407975]
13. Jansson LM, Di Pietro JA, Elko A, Williams EL, Milio L, Velez M. Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: a comparison of fetal neurobehaviors and infant outcomes. Drug Alcohol Depen. 2012; 122:213–9.
14. Wachman EM, Hayes MJ, Brown MS, Paul J, Harvey-Wilkes K, Terrin N, et al. Association of OPRM1 and COMT Single-Nucleotide Polymorphisms With Hospital Length of Stay and Treatment of Neonatal Abstinence SyndromeSNPs and Outcomes in Neonatal Abstinence Syndrome. JAMA. 2013; 309:1821–7. [PubMed: 23632726]
15. Chan D, Klein J, Koren G. New methods for neonatal drug screening. NeoReviews. 2003; 4:e236–e44.
16. Montgomery D, Plate C, Alder SC, Jones M, Jones J, Christensen RD. Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium. J Perinatol. 2006; 26:11–4. [PubMed: 16281047]
17. Coyle M, Ferguson A, LaGasse L, Liu J, Lester B. Neurobehavioral effects of treatment for opiate withdrawal. Arch Dis Child-Fetal. 2005; 90:F73–F4.
18. Velez ML, Jansson LM, Schroeder J, Williams E. Prenatal methadone exposure and neonatal neurobehavioral functioning. Pediatr Res. 2009; 66:704–9. [PubMed: 19690513]
19. Liu J, Bann C, Lester B, Tronick E, Das A, Lagasse L, et al. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics. 2010; 125:e90–e8. [PubMed: 19969621]
20. Lester BM, Lagasse LL. Children of addicted women. J Addict Dis. 2010; 29:259–76. [PubMed: 20407981]
21. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. Addict Dis. 1975; 2:141–58. [PubMed: 1163358]
22. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. Clin Pediatr. 1975; 14:592–4.
23. Green M, Suffet F. The Neonatal Narcotic Withdrawal Index: a device for the improvement of care in the abstinence syndrome. Am J Drug Alcohol Ab. 1981; 8:203–13.
24. Zahorodny W, Rom C, Whitney W, Giddens S, Samuel M, Maichuk G, et al. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. J Dev Behav Pediatr. 1998; 19:89–93. [PubMed: 9584937]
25. Hudak ML, Tan RC. Neonatal drug withdrawal. Pediatrics. 2012; 129:e540–60. [PubMed: 22291123]
26. Eidelman AI, Schanler RJ, Johnston M, Landers S, Noble L, Szucs K, et al. Breastfeeding and the use of human milk. Pediatrics. 2012; 129:e827–e41. [PubMed: 22371471]
27. Jansson LM. ABM clinical protocol# 21: Guidelines for breastfeeding and the drug-dependent woman. Breastfeeding Med. 2009; 4:225–8.
28. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. Pediatrics. 2006; 117:e1163–9. [PubMed: 16740817]
29. Isemann B, Meinzen-Derr J, Akinbi H. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. J Perinatol. 2011; 31:25–9. [PubMed: 20508596]
30. Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarko L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. Acta Paediatr. 2013; 102:1060–6. [PubMed: 23909865]
31. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: non-pharmacologic care. J Addict Med. 2008; 2:113. [PubMed: 19727440]

32. D'Apolito K. Comparison of a rocking bed and standard bed for decreasing withdrawal symptoms in drug-exposed infants. MCN Am J Matern Child Nurs. 1999; 24:138–44. [PubMed: 10326317]
33. Saiki T, Lee S, Hannam S, Greenough A. Neonatal abstinence syndrome-postnatal ward versus neonatal unit management. Eur J Pediatr. 2010; 169:95–8. [PubMed: 19440732]
34. Hodgson ZG, Abrahams RR. A rooming-in program to mitigate the need to treat for opiate withdrawal in the newborn. J Obstet Gynaecol Can. 2012; 34:475–81. [PubMed: 22555142]
35. American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. Pediatrics. 1998; 101:1079–88.
36. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Db Syst Rev. 2010; 10
37. O'Grady MJ, Hopewell J, White MJ. Management of neonatal abstinence syndrome: a national survey and review of practice. Arch Dis Child-Fetal. 2009; 94:F249–F52.
38. Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. J Perinatol. 2006; 26:15–7. [PubMed: 16355103]
39. Barrett DA, Barker DP, Rutter N, Pawula M, Shaw PN. Morphine, morphine-6-glucuronide and morphine-3-glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. Br J Clin Pharmacol. 1996; 41:531–7. [PubMed: 8799518]
40. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Brit J Anaesth. 2004; 92:208–17. [PubMed: 14722170]
41. Nandakumar N, Sankar V. What is the best evidence based management of neonatal abstinence syndrome? Arch Dis Child-Fetal. 2006; 91:F463.
42. Kraft WK, van den Anker JN. Pharmacologic management of the opioid neonatal abstinence syndrome. Pediatr Clin North Am. 2012; 59:1147–65. [PubMed: 23036249]
43. Yang F, Tong X, McCarver DG, Hines RN, Beard DA. Population-based analysis of methadone distribution and metabolism using an age-dependent physiologically based pharmacokinetic model. J Pharmacokinet Pharmacodyn. 2006; 33:485–518. [PubMed: 16758333]
44. Lainwala S, Brown ER, Weinschenk NP, Blackwell MT, Hagadorn JI. A retrospective study of length of hospital stay in infants treated for neonatal abstinence syndrome with methadone versus oral morphine preparations. Adv Neonatal Care. 2005; 5:265–72. [PubMed: 16202968]
45. Backes CH, Backes CR, Gardner D, Nankervis CA, Giannone PJ, Cordero L. Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting. J Perinatol. 2012; 32:425–30. [PubMed: 21852772]
46. Bhatt-Mehta V, Ng CM, Schumacher RE. Effectiveness of a Clinical Pathway With Methadone Treatment Protocol for Treatment of Neonatal Abstinence Syndrome Following In Utero Drug Exposure to Substances of Abuse. Pediatr Crit Care Med. 2014; 15:1–8. [PubMed: 24201859]
47. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. Cochrane Db Syst Rev. 2009; 3
48. Kraft WK, Gibson E, Dysart K, Damle VS, Larusso JL, Greenspan JS, et al. Sublingual buprenorphine for treatment of neonatal abstinence syndrome: a randomized trial. Pediatrics. 2008; 122:e601–7. [PubMed: 18694901]
49. Kraft WK, Dysart K, Greenspan JS, Gibson E, Kaltenbach K, Ehrlich ME. Revised dose schema of sublingual buprenorphine in the treatment of the neonatal opioid abstinence syndrome. Addiction. 2011; 106:574–80. [PubMed: 20925688]
50. Cober MP, Johnson CE. Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. Am J Health Promot. 2007; 64:644–6.
51. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics. 2009; 123:e849–56. [PubMed: 19398463]
52. Leikin JB, Mackendrick WP, Maloney GE, Rhee JW, Farrell E, Wahl M, et al. Use of clonidine in the prevention and management of neonatal abstinence syndrome. Clin Toxicol. 2009; 47:551–5.
53. Xie HG, Cao YJ, Gauda EB, Agthe AG, Hendrix CW, Lee H. Clonidine clearance matures rapidly during the early postnatal period: a population pharmacokinetic analysis in newborns with neonatal abstinence syndrome. J Clin Pharmacol. 2011; 51:502–11. [PubMed: 20484620]

54. Surran B, Visintainer P, Chamberlain S, Kopcza K, Shah B, Singh R. Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome. A prospective randomized clinical trial. J Perinatol. 2013; 33:954–9. [PubMed: 23949834]

55. McVay, D.; Schiraldi, V.; Ziedenberg, J. Treatment Or Incarceration?: National and State Findings on the Efficacy and Cost Savings of Drug Treatment Versus Imprisonment. Justice Policy Institute; 2004.

56. Jones HE, Jansson LM, O'Grady KE, Kaltenbach K. The relationship between maternal methadone dose at delivery and neonatal outcome: Methodological and design considerations. Neurotoxicol Teratol. 2013; 39:110–5. [PubMed: 24099621]

57. Campa D, Gioia A, Tomei A, Poli P, Barale R. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther. 2008; 83:559–66. [PubMed: 17898703]

58. Rakvag TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain. 2008; 4:64. [PubMed: 19094200]

59. Truven Health Analytics. Micromeex Solutions Redbook. [January 30, 2014] http://micromedex.com/redbook

60. Wiles JR, Vinks AA, Akinbi H. Federal legislation and the advancement of neonatal drug studies. J Pediatr. 2013; 162:12–5. [PubMed: 23110945]

Abbreviations

AAP	American Academy of Pediatrics
COMT	catechol-O-methyltransferase
OPRM1	mu-opioid receptor
NAS	Neonatal Abstinence Syndrome
PD	Pharmacodynamics
PK	Pharmacokinetics