

Neonatal Abstinence Syndrome in 2019: Learning From Our Mistakes

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KAAP Progress in Pediatrics
October 11, 2019



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Objectives

- Discuss the increased incidence of NAS
- Describe the common signs and symptoms of NAS
- Review the most common maternal substances causing neonatal withdrawal and onset of symptoms
- Discuss pharmacologic and non-pharmacologic methods of managing neonatal withdrawal

Why is NAS a problem?

- Increasing number of women and fetuses affected
 - Illicit drugs
 - Prescription pain medications
 - Mental illness
- Recent stats
 - Every 15 minutes a baby is born with NAS
 - Hospital costs for NAS have grown more than 6X since 2004
 - Resulted in ~\$2 billion in excess costs among Medicaid financed deliveries
- Opiate pain relievers
 - Now responsible for more overdose deaths than cocaine and heroin combined
 - More deaths than motor vehicle collisions

What is NAS?

- Clinical diagnosis: Constellation of physiologic and neurobehavioral signs
- Sudden discontinuation of fetal exposure to substances used/abused during pregnancy
- Pathophysiology not completely understood
 - Immature neurologic development
 - Impaired neurologic processing
 - Complex materno-feto-placental pharmacokinetics
- Density/affinity of neonate opioid receptors as good as adults
- Lack of opioids in a chronically stimulated state increases activity in opioid receptors → increased production of neurotransmitters → symptoms of NAS

What are the signs and symptoms of NAS ?

- Nonspecific
- Vary among patients
- May NOT correlate with the dose or duration of exposure
- Physiology primarily involves
 - Central Nervous System
 - Gastrointestinal
 - Respiratory System
 - Autonomic Nervous System

What are the signs and symptoms of NAS ?

Central Nervous System

- Hypertonia
- Tremors
- Hyperreflexia
- Irritability
- Restlessness
- High pitched cry
- Sleep disturbances
- Seizures

Autonomic Nervous System

- Sweating
- Low-grade fever
- Nasal stuffiness
- Excessive sneezing
- Yawning
- Skin mottling

What drugs are we talking about?

• Narcotics are the most frequent

- Heroin
- Methadone
- Morphine
- Oxycodone
- Codeine
- Buprenorphine

• Stimulants

- Methamphetamines
- Cocaine

• Depressants and Sedative

- Ethanol

• Antidepressants

• Anxiolytics

Why do opioids accumulate in the fetus?

- Low molecular weights
- Water soluble
- Lipophilic
- Easily transferable across the placenta
- Increases with gestational age
- Withdrawal worse in infants
 - Ease of crossing blood brain barrier
 - Prolonged half-life of these drugs in fetus

Why Do We Treat Mothers?

- **Abrupt discontinuation of opioids in a dependent pregnant woman can result in**
 - Preterm labor
 - Fetal distress
 - Fetal demise
- **Current standard of care :**
 - Methadone
 - Buprenorphine
- **Treatment**
 - Decreases illicit drug use
 - Optimizes obstetric care
 - Improves fetal outcomes
 - Increases incidence of NAS

ACOG Opioid use and opioid use disorder in pregnancy Committee Opinion No. 711

- Early Universal Screening
- Referral for treatment of pregnant women with opioid use/abuse
- Avoid or minimize the use of opioids for pain management
- Opioid agonist preferred over medically supervised withdrawal
- Infants born to women who used opioids during pregnancy should be monitored
- Consider modifying prenatal care (expanded STI testing, additional ultrasounds to assess fetal weight, consultations as needed)

Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e81–94.



ACOG Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711

- Ensure opioids are appropriately indicated
- Discuss risks and benefits of use during pregnancy
- Set treatment goals
- Take thorough history of substance use
- Review Prescription Drug Monitoring Program (PDMP)
- Encourage breastfeeding if no contraindications
- Ensure access to adequate postpartum psychosocial support services
- Contraceptive counseling and access should be routine part of substance use disorder treatment

Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e81–94.



When Do We See Onset of Withdrawal?

Drug	Approximate Time to Onset of Withdrawal Symptoms
Methamphetamines	Usually no symptoms, sometimes neurobehavioral abnormalities
Cocaine	Usually no signs but sometimes neurobehavioral abnormalities around 48-60 hrs (decreased arousal)
Marijuana	Usually no clinical withdrawal
Alcohol	3-12 hours
SSRIs	Several hours to several days
Heroin	Within 24 hours
Opioids	24 to 36 hours but up to 5-7 days
Methadone/Buprenorphine	3 days usually, up to 5-7 days
Barbiturates	4-7 days (range 1-14 days)

When and how do we monitor for NAS?

- **NAS Scoring Systems**
- **Eat, Sleep, Console**
- **Neonatal Drug Withdrawal Scoring System (Lipsitz Tool)**
- **Modified Finnegan most common**
 - Can be used for opioid and nonopioid withdrawal assessment
 - 20 most common signs and grouped them into categories
 - Signs ranked according to pathologic significance
 - Strong interobserver variability
 - Assists in monitoring, titrating, terminating medical therapy

Eat, Sleep, Console

A Novel Approach to Assessing Infants With Neonatal Abstinence Syndrome
Matthew R. Grossman, Matthew J. Lipshaw, Rachel R. Osborn, Adam K. Berkowitz
Hospital Pediatrics Jan 2018, 8 (1) 1-6;



What do we use to treat NAS? Non-Rx

- Gentle handling
- Ad lib demand feedings
- Swaddling
- Minimal stimulation
- Kangaroo care, holding, cuddling, manual rocking, pacifier
- Capture infant when irritable before cycle of irritability begins
- Active maternal participation and rooming-in if appropriate



Feeding and nutritional support

- Opioid receptors concentrated in CNS and GI tract
- Poor feeding, vomiting, diarrhea, dehydration
 - Can lead to poor weight gain
- Drug exposed infants cannot relax, breath, suck simultaneously
- Flexion with containment and swaddling provides relaxation and comfort
 - Creates a sense of control
 - Decreases disorganization

Hudak ml, Tan rc et al. neonatal drug withdrawal.
Pediatrics 2012;129 (2)P e540-560.



Challenges in encouraging optimal nutrition:

- State instability
 - Hyper-sensitive to surroundings
 - Easily agitated
- Atypical suck
 - Disorganized suck, latch, swallow
 - Prolonged sucking bursts with few pauses
 - Not meeting volume minimums
 - Taking >30-45 minutes to feed
- Increased caloric needs
 - Hypermetabolic
 - Increased output/losses
- Hyperphagia
 - Volumes >190-200 ml/kg/day
 - Increased air intake
 - Prolonged sucking bursts, "ravenous"
 - Increased weight loss
- Projective vomiting
- Regurgitation
 - During feeding
 - Not related to burping

Martinez A et al. Hyperphagia in neonates withdrawing from methadone.
Arch dis child fetal neonatal ed. 1998;80 (3):F178-182.



Feeding

- Feedings should be led by infant with active participation of caregiver
- Cue based
- Pace and allow for breaks as needed
- Avoid distractions, interference, multi-tasking
- Benefits of breastfeeding
- Barriers to breastfeeding
- If breastmilk not available, *“Expert opinions recommend additional calories in a lactose-free formula..”*.

Casper, T. et al. Advances in Neonatal Care • Vol. 14, No. 6 • pp. 376-380



When do we start medical therapy?

- When not responsive to nonpharmacologic interventions AND
- Traditional scoring assessment
 - 3 consecutive scores ≥ 8 or average of 3 consecutive scores ≥ 8 *OR*
 - 2 consecutive scores ≥ 12 or average of 2 consecutive scores ≥ 12
- Functional assessment
 - Eat < 1 oz or breastfeed poor
 - Sleep < 1 hour
 - Consoling takes > 10 minutes
- Serious clinical signs, i.e. seizures, dehydration, etc



How do we treat with medical therapy?

- No standardized regiment for medical management
- Important to “capture” patient symptoms
- Delays in administration of Rx therapy associated with
 - Higher morbidity
 - Longer hospital stay
- Having a standardized protocol
 - Decrease length of stay
 - Decrease medication use
 - May be more important than choice of specific opioid

What medicine(s) do we use to treat NAS?

- Paregoric or tincture of opium no longer used
 - Toxic ingredients and high alcohol content
- Sedatives not useful because of prolonged half-life and complications
 - Diazepam and chlorpromazine
- Morphine most commonly preferred medication
 - Short half life, must be provided Q3-4 hours
 - Dose can be escalated fairly quickly
 - Weaning has to be gradual

What medicine(s) do we use to treat NAS?

- If optimal response not attained with max dose, consider additional medications
- Methadone
 - Long half-life
- Phenobarbital
 - For non-opioid NAS
- Clonidine as adjunctive therapy
 - Theoretical risk of hypotension, bradycardia
- Buprenorphine?

Methadone vs morphine

- 117 infants randomized to treatment with methadone or morphine
- Methadone associated with reduced LOS and length of treatment
- Adjusted for study site and type of maternal opioid
- Conclusion: Methadone more effective than morphine for NAS

Buprenorphine for treatment of NAS

- Single site, double-blind, double-dummy clinical trial
- Randomly assigned 63 term infants exposed to opioids in utero and signs of NAS
- Received either
 - Sublingual buprenorphine
 - Oral morphine
 - Symptoms not controlled with max dose of opioid received adjunctive phenobarbital
- End points
 - Primary: duration of treatment
 - Secondary: LOS, percentage of infants who required phenobarbital, safety

Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. N Engl J Med 2017;376:2341-8.



Buprenorphine for treatment of NAS

- Used MOTHER NAS scale (modified Finnegan)
- Scored Q4 hours for minimum 72 hours
- Threshold for treatment was sum of 3 scores ≥ 24 or single score of ≥ 12
- Randomized randomly in 1:1 ratio to morphine or buprenorphine
- Randomization stratified according to maternal exposure to methadone or buprenorphine and maternal intention to breastfeed or bottle feed

Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. N Engl J Med 2017;376:2341-8.



Buprenorphine for treatment of NAS

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Buprenorphine for treatment of NAS

- Similar safety profile
- Infants in morphine group had a lower respiratory rate
- Longer interval between doses of buprenorphine may allow for future outpatient setting
- Did not include in utero benzodiazepine exposure, clinical trial investigating
- Author's conclusion:
 - Sublingual buprenorphine was significantly more effective than oral morphine in decreased duration of treatment for NAS and LOS

Kraft WK, Adeniyi-Jones SC, Chervoneva I, et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. N Engl J Med 2017;376:2341-8.



AAP called for all centers that might care for infants at risk for NAS to establish guidelines for the following:

- 1) Screening for maternal substance use**
- 2) Nonpharmacologic treatment of infants with NAS**
- 3) Scoring signs of NAS**
- 4) Breastfeeding**
- 5) Pharmacologic management**
- 6) Duration of observation of exposed infants**

Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5):e20153835



Improving care for NAS

- Multicenter, multistate quality improvement collaborative**
- Infants requiring pharmacologic treatment for NAS**
- 2012-2014**
- Cross-sectional audits of 199 VON participating centers**
- Hospitals assessed**
 - Institutional policies**
 - Length of pharmacologic treatment**
 - Length of hospital stay (LOS)**

Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5):e20153835



Improving care for NAS

- Decrease in median length of therapy from 16 days to 15 days
- Decrease length of stay from 21 days to 19 days

Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5):e20153835



Improving care and cost of NAS

FINANCIAL

- Medicaid was the primary payer for ~80% of infants with NAS
- Using 2012 estimates, reducing LOS by 2 days nationwide

▪\$170 MILLION

SOCIETAL

- ~30% of infants were not discharged with their mothers

NEED Primary prevention strategies

- reduce unnecessary prescribing to women of childbearing age
- decrease unplanned pregnancies by including access to contraceptive care as part of substance abuse programs

Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5):e20153835



Management Consensus

- Monitor in the hospital at least 5-7 days
- First line medication: morphine
- Considering adjuvant therapies with clonidine versus methadone
- Weaning of medications if no increased symptoms in 24-48 hours
- Monitor in the hospital for 48 hours after the last dose of morphine
- Consider discharge home on methadone
- Do not discharge home on morphine or clonidine
- Oh Canada?

Who can breastfeed?

- No restrictions on breastfeeding for mothers on methadone
 - Breast milk contains only minimal quantities of methadone and buprenorphine
 - Amount is too small to treat NAS, but gradual weaning is advised
- Despite this, small percentage of mothers breastfeed
- High concentrations of hydrocodone and oxycodone in breast milk and reduced clearance of medications in some neonates
 - Can lead to sedation in infants
- Breastfeeding is not contraindicated for most psychotropic medications
- Breastfeeding IS contraindicated if mother is taking illicit drugs, polydrug abuse, or HIV infection

Academy of Breastfeeding Medicine Recommendations and Maternal Drug Exposure

- Encourage breastfeeding if:
 - Mom is in treatment for substance abuse.
 - Substance abuse treatment provider endorses mother's sobriety prenatally
 - Plans to continue in treatment program postpartum
 - Abstinent from illicit drug use for 90 days prior to delivery and demonstrates ability to maintain sobriety in an outpatient setting.
 - Negative drug screen at delivery except for prescribed meds.
 - Received consistent prenatal care.
 - No medical contraindication to breastfeeding (HIV, certain psychiatric medications)
 - Stable on methadone or buprenorphine (regardless of dose).

Where should these babies be monitored?

- Couplet care or rooming in encouraged

Criteria for Discharge

- Scores <8, responsive to nonpharmacologic interventions, and symptoms stable for 72 hours
- If mother remains on methadone, must be enrolled in methadone or chronic pain clinic
- Social work and DFS involved when appropriate
- Safe home environment, reliable parent(s), cleared by DFS
- Parents able to demonstrate competency with cares and dosing while rooming in
- Reliable transportation for follow-up appointments
- Primary care physician identified and contacted, willing to assume care of infant
- Pharmacy/insurance support for obtaining outpatient medications must be identified and secured

What have we covered re: NAS?

- Constellation of physiologic and neurobehavioral signs
- Sudden discontinuation of fetal exposure to substances used/abused during pregnancy
- Finnegan scoring system commonly used
 - Eat, Sleep, Console needs more study
- Nonpharmacologic treatment is always first option
- Morphine is most commonly used drug for NAS
 - Buprenorphine being studied
- Breastfeeding not contraindicated in most cases



Addressing the Opioid Epidemic

SUD = substance abuse disorder

OOD = opioid use disorder

MAT = medication assisted treatment



Align and improve financial incentives to ensure access to evidence-based OUD treatment

- **Keep Medicaid strong**
 - Expansion
 - Without restrictions
- **Access to SUD treatment**
 - Inadequate reimbursement limits access
 - Medication and therapy together more effective
 - Several states do not cover these treatments through Medicaid
 - Medicare has no comprehensive SUD treatment benefit
- **Keeping families safely together during a parent's SUD treatment**
 - Improved outcomes for both parents and children



Incentivize more providers to treat SUD

- Ensure adequate supply of providers
- ~2.1 million Americans with untreated opioid use disorders
- Incentivize addiction professionals to increase access
 - Increase behavioral health workforce
 - Rural and underserved areas
 - Telehealth
 - Integrated care models

Address the maternal-child health impact

- Overdose and suicide, directly linked to rise in OUD, are now leading cause of maternal mortality in a growing number of states
- Increasing access to evidence-based treatment for pregnant and parenting women will improve maternal and child outcomes
- MAT improves adherence to prenatal care
- Reduces risk of obstetric complications among pregnant women
- Threats of punishment drive pregnant and parenting women away from vital prenatal care and SUD treatment
- Non-punitive public health approaches result in better outcomes

Address the maternal-child health impact

- NAS from medication assisted therapy during pregnancy is preferable to other outcomes
 - Maternal relapse
 - Maternal or fetal death
- Focus must remain on mother-baby relationship
- Account for factors that drive disparities in access to treatment for pregnant and parenting women with OUD
 - Biological
 - Environmental
 - Social

NAS and Foster Care

- >1/3 of 270,000+ children entering foster care in 2016: parent SUD
- Need access to treatment for whole family
- Prevent unnecessary foster care placements
- Implementation of the [Family First Prevention Services Act](#)
- Residential SUD treatment facility can treat parent and child together

Reduce the Stigma Related to SUD

- Address stigma with state prevention strategy
 - Educate public and healthcare providers about addiction
 - Chronic brain disease
 - Can be effectively treated with evidence-based interventions
- SUD often coexist with other mental health disorders or trauma
 - Ensure access to appropriate trauma-informed mental health services
 - Alleviate stigma associated with seeking treatment

Reduce administrative burden associated with providing patients effective treatment

- Obtaining prior authorization is overly burdensome
- Delays treatment to life-saving care
 - Some private insurers have already lifted prior authorizations
- Discontinue policies that interfere in practice of medicine
 - Engage providers rather than mandating education and limits on opioid Rx
 - Providers should partner with federal and state government
 - Increase public awareness
 - Increase provider training and education

Advance research to support prevention and treatment of SUD

- Optimal doses and duration
 - Differences in metabolism in pregnant and breastfeeding women
- Treatment interventions that address familial impact
- Optimal treatment of infants born with NAS
 - Long-term outcomes
- Substantial evidence exists on the lifelong health consequences of trauma in childhood.
 - Many are children of parents struggling with OUD
- Threats of punishment drive pregnant and parenting women away from vital prenatal care and SUD treatment
- Non-punitive public health approaches result in better outcomes

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