Neonatal Opiate Withdrawal: A Review and Update

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May 15th, 2013

Objectives

- Definitions and Classification of Opioids
- Opioid Pharmacology
- Epidemiology of opiate abuse
- Discuss opioid-maintenance treatment in pregnancy
  - ACOG recommendations
  - Literature review
- Review neonatal abstinence syndrome
  - Provide overview of current treatment strategies
- NAS Research
- Conclusions

Definitions

- Opium
  - Refers to a mixture of alkaloids from the poppy seed
- Opiates
  - Consist of the *naturally* occurring compounds extracted from opium (*Papaver somniferum)*
    - morphine, codeine, heroin
- Opioids
  - Natural *and* synthetic substances with morphine-like activity

Opioids: Pharmacology

- Can further be classified by their actions
  - agonist (morphine, methadone)
  - agonist/antagonist (Suboxone- buprenorphine and Narcan)
  - partial agonist (Subutex- buprenorphine)
  - antagonist (Narcan)

Trescot et al; Pain Physician 2008

Opioids: Pharmacology

- Have varying intrinsic affinity and efficacy at specific receptors (mu, kappa, and delta)
  - Affinity
    - a measure of the strength of interaction between a compound binding to its receptor
  - Efficacy
    - a measure of the strength of activity or effect from this binding at the receptor

Trescot et al; Pain Physician 2008

Opioids: Pharmacology

- Opiate agonists
  - Have *both* affinity and efficacy
    - Methadone, morphine
- Opiate antagonists
  - have affinity but no efficacy
    - Narcan
- Partial opiate agonists
  - have affinity but only partial efficacy
    - Subutex

Opioid Pharmacology

Table 1. *Analgesic effects at opioid receptors.*

	Mu (μ)	Delta (δ)	Kappa (κ)
	• Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	• Analgesia, spinal analgesia	• Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous Peptides			
Enkephalins	Agonist	Agonist	
β-Endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Antagonists			
Naloxone	Antagonist	Weak Antagonist	Antagonist
Naltrexone	Antagonist	Weak Antagonist	Antagonist

Modified from Miller's Anesthesia (4)

Opioids: Pharmacology

- Opioid receptors located on the presynaptic terminals of nociceptive C-fibers and A delta fibers
- Activation by an opioid agonist
  - Indirectly inhibits voltage-dependent calcium channels
    - Decreases cAMP levels
    - Blocks the release of pain neurotransmitters (glutamate, substance P, calcitonin gene-related peptide) from the nociceptive fibers resulting in analgesia

Trescot et al; Pain Physician 2008

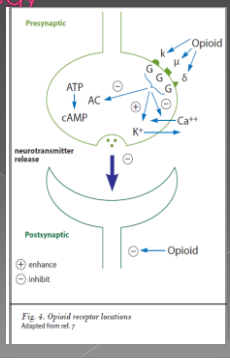
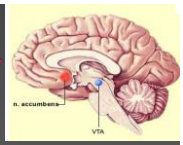


Fig. 4. Opioid receptor locations
Adapted from ref. 7

Opioids: Pharmacology

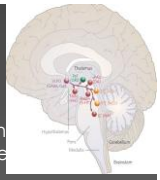


Opioids and endogenous opioids

- Activate presynaptic receptors on GABA neurons
  - Inhibits the release of GABA in the ventral tegmental area
  - Allows dopaminergic neurons to fire more vigorously
    - Extra dopamine in the nucleus accumbens is intensely pleasurable
      - Dopamine seems to strengthen the inherent rewarding characteristics of drugs of abuse

Trescot et al; Pain Physician 2008

Opioids: Pharmacology



- Neurobiological changes play a role in the progression of opioid dependence
- Locus coeruleus
  - The primary source of almost all noradrenergic afferents in the brain
    - Norepinephrine may play a role in encouraging drug-seeking behaviors and eventual dependence
    - Opioid mu agonists acutely *inhibit* the activity of the locus coeruleus
      - Inhibits the release of noradrenaline at synaptic terminals

Benich et al; Prim Care Clin Office Pract (2011)

Opioids: Pharmacology

- With chronic opioid exposure, tolerance develops as the rate of noradrenaline release over time increases toward normal
- Abrupt discontinuation of exogenous opioids
  - Results in supranormal release of noradrenaline
    - Produces the autonomic and behavioral signs and symptoms characteristic of withdrawal

PEDIATRICS Volume 129, Number 2, February 2012

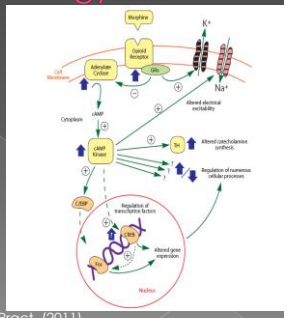
Opioids: Pharmacology

- Opioid withdrawal syndrome
  - Thought to be due to hyperactivity in the locus coeruleus once opiate inhibition is discontinued
  - a2-adrenergic medications (clonidine) for assistance in the treatment of opioid withdrawal symptoms
    - Provides symptom relief by decreasing some of the noradrenergic hyperactivity in the central nervous system
    - Has been use as an adjunct therapy to opioids for NAS

Benich et al; Prim Care Clin Office Pract (2011)
Agathe et al; Pediatrics 2009

Opioids: Pharmacology

- Neurobiologic changes contributing to opioid withdrawal syndrome
  - Changes in G protein–coupled receptors
  - Variations in transcription and translation
  - Increased activity of cyclic adenosine monophosphate second messenger channels



Benich et al; Prim Care Clin Office Pract (2011)

Opioids: Pharmacology

- Pure opioid agonists stimulate μ receptors and are the most potent analgesics
  - Morphine, Methadone, hydromorphone, and fentanyl
    - As the dose is increased, analgesia theoretically occurs in a log-linear fashion
    - The degree of analgesia induced is limited only by intolerable dose-related adverse effects
    - Full agonists are *controlled substances* because they can produce effects similar to the drugs of abuse they are used to replace

Opioids: Pharmacology

Table 2: *D.E.A schedules of controlled drugs.*

Schedule	Criteria	Examples
I	No medical use; high addiction potential	Heroin, marijuana, PCP
II	Medical use; high addiction potential	Morphine, oxycodone, methadone, fentanyl, amphetamines
III	Medical use; moderate addiction potential	Hydrocodone, codeine, anabolic steroids
IV	Medical use; low abuse potential	Benzodiazepines, meprobamate, butorphanol, pentazocine, propoxyphene
V	Medical use; low abuse potential	Buprenex, Phenergan with codeine

Modified from ref. 10

Opioids: Pharmacology

- Opioid agonists/antagonists and opioid partial agonists (buprenorphine, nalbuphine)
  - Exhibit a ceiling effect on the degree of analgesia that they can produce
  - The respiratory depressant effects of partial agonists are not completely reversed with naloxone

Trescot et al; Pain Physician 2008

Subutex

- Buprenorphine (Buprenex)
  - Partial mu receptor agonist that also possesses some antagonist properties at the k receptor
  - High affinity for (1000- fold higher than morphine)and a slow dissociation from mu-opioid receptors
    - Blocks other opioids temporarily
    - Can precipitate acute withdrawal by displacing other opioids from the mu receptor

Benich et al; Prim Care Clin Office Pract 38 (2011)

Subutex (Buprenorphine)-Sublingual

- Absorbed through GI and mucosal membranes
  - Oral formulation has poor bioavailability due to extensive metabolism in the gastrointestinal tract
  - Bioavailability ranging from 30 to 50 percent of the intravenous dose
  - Maximal plasma concentration is reached within one hour
  - Metabolized primarily in the liver via the cytochrome P450
    - Mean plasma elimination half-life is 37 hours

Benich et al; Prim Care Clin Office Pract 38 (2011)

Suboxone

Buprenorphine with naloxone

- 4:1ratio for sublingual administration
  - 2 mg/ 0.5 mg and 8 mg/2 mg
  - Used to prevent abuse through injection of the medication that is intended to be used sublingually
  - This combination is effective because naloxone has minimal efficacy when taken sublingually, but it exerts full antagonist properties if injected

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Buprenorphine May Not Be as Safe as You Think: A Pediatric Fatality From Unintentional Exposure

Hong K. Kim, Monica Smiddy, Robert S. Hoffman and Lewis S. Nelson

Pediatrics 2012;130;e1700; originally published online November 5, 2012;
DOI: 10.1542/peds.2012-1342

- Case mortalities have been reported in both adults and children
  - Majority of adult mortalities can be explained by poly-substance abuse (benzodiazepines)
  - In children, buccal absorption is likely to be the major route of exposure
    - more common for children to either chew or suck on tablets
    - bioavailability from the buccal route is lower than by the sublingual route (28% vs 51%)
  - *The ceiling effect on respiratory depression does not seem to hold true in these cases*

Epidemiology

Number of unintentional exposures in children is increasing

- Data from the American Association of Poison Control Centers
  - Buprenorphine exposures in children younger than 6 years old increased dramatically
    - 2002 (2 cases)
    - 2008 (907 cases)
  - Methadone exposures (same age group) doubled from 155 cases to 332 cases during the same 6- year period
- In 2010, the number of buprenorphine exposures exceeded methadone exposure in children <6 years old

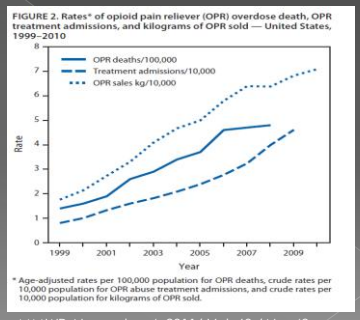
Kim et al; Pediatrics 2012
Bronstein et al; 2010 National Poison Data System (NPDS): 28th Annual Report. Clin Toxicol (Phila). 2011

Epidemiology

- Death from opioid pain relievers (OPR) is an epidemic in the United States
- Sales of OPR quadrupled between 1999 and 2010
  - Enough OPR were prescribed IN 2010 to medicate every American adult with a standard pain treatment dose of 5 mg of hydrocodone (Vicodin) taken every 4 hours for a month
  - Abuse of OPR costs health insurers approximately $72.5 billion annually in health-care costs
  - State-based prescription drug monitoring program records and insurance claims information can identify and address inappropriate prescribing and use by patients
  - State laws and regulations based on these data need to be enacted, enforced, and rigorously evaluated

MMWR. November 4, 2011/ Vol. 60 / No. 43

Epidemiology



MMWR. November 4, 2011/ Vol. 60 / No. 43

Epidemiology

- Among pregnant women aged 15 to 44, 5.0 % were current illicit drug users
  - Based on data averaged across 2010 and 2011
  - Rate among women in this age group who were *not* pregnant (10.8 %)
  - This rate was not significantly different from the rate averaged across 2008-2009 (4.5 %)

Substance Abuse and Mental Health Services Administration; 2011

Epidemiology

- Marijuana remains the most commonly used illegal drug, followed by cocaine
  - Wong et al; International Journal of Gynecology and Obstetrics 114 (2011) 190–202
- Under-recognition of prenatal drug abuse is common
  - Azadi et al; American Journal of Obstetrics & Gynecology (2008)

FROM THE AMERICAN ACADEMY OF PEDIATRICS

TABLE 1 Major Drugs of Abuse[a]

Opioids	CNS Stimulants	CNS Depressants	Hallucinogens
Agonists	Amphetamines	Alcohol	Indolealkylamines (LSD, psilocin, psilocybin, DMT, DET)
Morphine	Dextroamphetamine (Dexedrine)	Barbiturates	Phenylethylamines (mescaline, peyote)
Codeine	Methamphetamine	Benzodiazepines	Phenylisopropylamines (MDA, MMDA, MDMA, MDEA)
Methadone	Amphetamine sulfate	Other sedative-hypnotics	Inhalants
Meperidine (Demerol)	Amphetamine congeners	Methaqualone (Quaalude)	Solvents and aerosols (glues, gasoline, paint thinner, cleaning solutions, nail polish remover, Freon)
Oxycodone (Percodan, OxyIR, Percolone, Roxicodone, Percocet, OxyContin)	Benzphetamine (Didrex)	Glutethimide (Doriden)	Nitrites
Propoxyphene (Darvon)	Diethylpropion (Tenuate)	Chloral hydrate	Nitrous oxide
Hydromorphone (Dilaudid)	Fenfluramine	Cannabinoids	
Hydrocodone (Lortab, Vicodin)	Phendimetrazine (Adipost, Bontril, Prelu-2)	Marijuana	
Fentanyl (Sublimaze)	Phentermine (Adipex-P, Zantryl)	Hashish	
Tramadol (Ultram, Ultracet)	Cocaine		
Heroin	Methylphenidate (Ritalin, Concerta)		
Antagonists	Pemoline (Cylert)		
Naloxone (Narcan)	Phenylpropanolamine		
Naltrexone (ReVia)	Phencyclidines		
Mixed Agonist-Antagonists	Nicotine		
Pentazocine (Talwin)			
Buprenorphine (Buprenex)			

DET, diethyltryptamine; DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; MDA, methylenedioxyamphetamine; MDEA, 3,4-methylenedioxyethamphetamine; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); and MMDA, 5-methoxy-4,5-methylenedioxyamphetamine.

Smoking and Pregnancy

Major public health problem

- with an estimated prevalence of 20–40%
  - has dangerous consequences for both mother and fetus
- Among pregnant opioid agonist-maintained women, the rate of smoking is *four times* higher than in the general population of pregnant women
  - Heavy tobacco smoking in opioid-maintained pregnant women is associated with adverse medical and developmental consequences for the newborn
    - Lower birth weight and length

Winklebaur et al; Euro Addict Research 2009

RESIDENTS' PAPERS www.AJOG.org

Universal screening for substance abuse at the time of parturition

Ali Azadi, MD; Gary A. Dildy III, MD

- Purpose:
  - To determine the prevalence of substance abuse in an inner city population at delivery admission by universal urine toxicology screening
- Study design:
  - Retrospective analysis of universal urine toxicology screening at admission for delivery on the LSU obstetric service at University Hospital in New Orleans
- Results:
  - Four hundred sixty-two women delivered during the first 4 months of 2005
  - Four hundred and sixteen (90%) had a urine screen performed and 79 (19%) screened positive for 1 or more substances

RESIDENTS' PAPERS www.AJOG.org

Universal screening for substance abuse at the time of parturition

Ali Azadi, MD; Gary A. Dildy III, MD

- Rates of a positive test by substance:
  - cocaine (3.1%)
  - amphetamines (2.4%)
  - barbiturates (2.1%)
  - opiates (2.6%)
  - THC (17.2%)
  - benzodiazepine (5.7%)
  - phencyclidine (0%)
- 19 % of the tested population screened positive for at least 1/7 substances at admission for delivery
  - Women who used illicit substances were older and of higher parity
  - Low birthweight and HIV were particularly prevalent in those who screened positive for cocaine and/or amphetamines

Universal screening for substance abuse at the time of parturition

Ali Azadi, MD; Gary A. Dildy III, MD

- A history of self-reported tobacco use was an indicator of illicit substance abuse
  - 59% of cocaine/amphetamine users had a history of tobacco use compared to 10% of nonusers
- Self-reported alcohol use during pregnancy was also correlated to illicit drug use
  - 27% among cocaine/ amphetamine users compared to only 1% of nonusers
- Preterm birth and low birthweight were more common among illicit drug users compared to nonusers

RESIDENTS' PAPERS www.AJOG.org

Universal screening for substance abuse at the time of parturition

Ali Azadi, MD; Gary A. Dildy III, MD

Authors Conclusions

- Universal screening at the time of delivery for maternal substance abuse *may be of limited* benefit for the current pregnancy
  - The timing of universal screening should be considered *earlier* in pregnancy for any real potential for benefit to be realized

Azadi et al; American Journal of Obstetrics & *Gynecology MAY 2008*

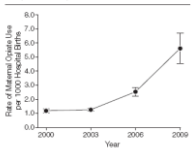
Neonatal Abstinence Syndrome and Associated Health Care Expenditures

United States, 2000-2009

Stephen W. Patrick, MD, MPH, MS
Robert E. Schumacher, MD
Brian D. Benneyworth, MD, MS
Elizabeth E. Krans, MD, MS
Jennifer M. McAllister, MD
Matthew M. Davis, MD, MAPP

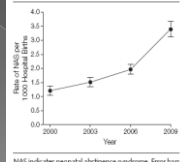
JAMA, May 9, 2012—Vol 307, No. 18
Corrected on May 16, 2012

Figure 2. Weighted National Estimates of the Rates of Maternal Opiate Use per 1000 Hospital Births per Year



Error bars indicate 95% CI. *P* for trend <.001 over the study period. The unweighted sample sizes for mothers diagnosed with and without antepartum opiate use are 987 and 833 494 in 2000; 1058 and 849 133 in 2003; 2160 and 879 910 in 2006; and 4563 and 816 654 in 2009, respectively.

Figure 1. Weighted National Estimates of the Rates of NAS per 1000 Hospital Births per Year



NAS indicates neonatal abstinence syndrome. Error bars indicate 95% CI. *P* for trend <.001 over the study period. The unweighted sample sizes for rates of NAS and for all other US hospital births are 2920 and 784 191 in 2000; 3761 and 890 582 in 2003; 5200 and 1 000 203 in 2006; and 9674 and 1 113 123 in 2009, respectively.

Patrick et al, *JAMA* 2012

Table 3. Mean Hospital Charges and Length of Stay for Neonatal Abstinence Syndrome vs All Other US Births

	Mean (95% CI)				*P* for Trend
	2000	2003	2006	2009	
Neonatal Abstinence Syndrome					
Unweighted sample, No.	2920	3761	5200	9674	
Length of stay, d	15.8 (14.2-17.3)	15.9 (14.5-17.3)	15.3 (14.6-16.0)	16.4 (15.8-17.1)	.06
Hospital charges, 2009 US $	39 400 (33 400-45 400)	47 900 (40 800-55 100)	44 600 (40 400-48 900)	53 400 (49 000-57 700)	<.001
All Other US Births					
Unweighted sample, No.	784 191	890 582	1 000 203	1 113 123	
Length of stay, d	3.1 (3.0-3.1)	3.2 (3.1-3.2)	3.2 (3.2-3.3)	3.3 (3.3-3.4)	<.001
Hospital charges, 2009 US $	6600 (5800-7300)	7300 (6900-7600)	8200 (7800-8600)	9500 (9000-9900)	<.001

Patrick et al, *JAMA* 2012

Table 4. Proportions of US Hospital Charges for Neonatal Abstinence Syndrome by Payer[a]

		Weighted % (95% CI)			
Year	Unweighted Sample, No.	Medicaid	Private Payer	Self-pay	Other Payer
2000	2920	68.7 (63.3-76.7)	18.2 (14.6-22.5)	8.7 (5.6-13.3)	4.4 (2.0-9.3)
2003	3761	69.9 (65.9-73.6)	19.8 (16.9-23.1)	6.5 (4.5-9.3)	3.8 (1.6-8.7)
2006	5200	73.7 (70.4-76.7)	19.0 (16.4-22.0)	5.5 (4.4-6.9)	1.9 (1.3-2.8)
2009	9674	77.6 (74.4-80.4)	17.6 (15.1-20.4)	2.9 (2.4-3.4)	2.0 (1.4-2.9)

[a] Percentages may not sum to 100 because of rounding.

Creanga et al; *Obstetrics and Gynecology* 2012

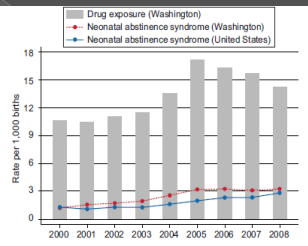


Fig. 1. Trends in prenatal drug exposure and neonatal abstinence syndrome in Washington State and the United States: 2000–2008.

Creanga. Maternal Drug Use and Neonatal Morbidity. Obstet Gynecol 2012.

Creanga et al; *Obstetrics and Gynecology* 2012

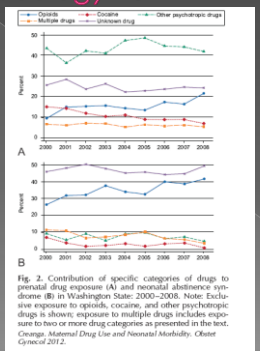


Fig. 2. Contribution of specific categories of drugs to prenatal drug exposure (A) and neonatal abstinence syndrome (B) in Washington State: 2000–2008. Note: Exclusive exposure to opioids, cocaine, and other psychotropic drugs is shown; exposure to multiple drugs includes exposure to two or more drug categories as presented in the text.
Creanga. Maternal Drug Use and Neonatal Morbidity. Obstet Gynecol 2012.

Creanga et al; *Obstetrics and Gynecology* 2012

Table 3. Associations Between Prenatal Drug Exposure and Neonatal Abstinence Syndrome and Perinatal Health Among Neonates in Washington State, 2000–2008

Perinatal Health Outcomes (N=669,451)	Drug-Unexposed (n=660,427) Mean (SD) or %	Drug-Exposed (n=9,024) Mean (SD) or %	Crude OR (95% CI)*	LBW-Adjusted OR (95% CI)†	Prematurity-Adjusted OR (95% CI)‡
Delivery-related associations					
Cesarean delivery	28.1	31.0	1.2 (1.0–1.3)		
Preterm delivery[†]	8.4	21.1	3.0 (2.8–3.1)		
Birth weight (g)[†]	3,385.9 (567.5)	3,062.6 (650.1)	−326.9 (−338.7 to −315.1)		
LBW*	5.7	16.6	3.4 (3.2–3.6)		
Disorders relating to short gestation and LBW	6.5	17.0	3.0 (2.9–3.2)		
LBW- or prematurity-confounded associations					
Length of birth hospitalization (d)	2.6 (6.3)	6.5 (12.0)	3.8 (3.7–4.0)	2.4 (2.3–2.6)	2.6 (2.5–2.8)
Feeding problems	3.4	10.4	3.4 (3.1–3.6)	2.2 (2.0–2.3)	2.2 (2.0–2.3)
Respiratory distress syndrome	1.3	3.4	2.7 (2.4–3.1)	1.2 (1.0–1.3)	1.2 (1.1–1.4)
Other respiratory conditions	6.7	15.6	2.6 (2.4–2.7)	1.8 (1.7–2.0)	1.8 (1.7–1.9)

SD, standard deviation; OR, odds ratio; CI, confidence interval; LBW, low birth weight.
The reference group for dichotomous outcomes in all models comprises neonates with a vaginal delivery, without LBW, delivered at or after term, without disorders relating to short gestation and LBW, feeding problems, respiratory distress syndrome, other respiratory conditions, respectively.
* Unadjusted model.
† Model adjusted only for LBW (birthweight data missing for 0.3% of cases).
‡ Model adjusted only for prematurity (gestational age data missing for 0.7% cases).

Illicit Drug Use In Pregnancy

- Lifestyle issues
  Prostitution , Theft, and violence
- Chronic untreated heroin use is associated with an increased risk of
  - Fetal growth restriction
  - Placental abruption
  - Fetal death
  - Preterm labor
  - Intrauterine passage of meconium

ACOG Committee Opinion No. 524, May 2012

Opiate addiction in Pregnancy

- Associated with:
  - Compulsive drug-seeking behavior
  - Physical dependence
  - Tolerance
- Once physical dependence has occurred, withdrawal symptoms occur if use is discontinued

ACOG Committee Opinion No. 524, May 2012

Opioid-Maintenance Therapy During Pregnancy

- Rationale
  - To prevent complications of illicit opioid use and narcotic withdrawal
  - Encourage prenatal care and drug treatment
  - Reduce criminal activity
  - Avoidance of the risks associated with a drug culture
- Comprehensive opioid-assisted therapy that includes prenatal care reduces the risk of obstetric complications

Opioid-Maintenance Therapy During Pregnancy

- The use of an antagonist, such as naloxone, to diagnose opioid dependence in pregnant women is *contraindicated*
  - Induced withdrawal may precipitate preterm labor/fetal distress
  - Naloxone should be used *only* in the case of maternal overdose to save the woman's life
- Medically supervised withdrawal from opioids in opioid-dependent women is *not* recommended during pregnancy
  - Withdrawal is associated with high relapse rates

ACOG Committee Opinion No. 524, May 2012

Treatment Options for Opioid Dependence in Pregnancy

- Methadone
  - Accepted since the late 1970s to treat opioid addiction during pregnancy
  - Currently the only opioid medication approved by FDA for MAT (Medication Assisted Treatment) in pregnant patients who are addicted to opioids
  - Reduces fluctuations in maternal serum opioid levels and protects the fetus from repeated withdrawal episodes
    - Long half-life enables once daily dosing

Substance Abuse and Mental Health Services Administration 2011

Opioid-Maintenance Therapy During Pregnancy: Methadone

- Prescribed and dispensed on a daily basis by a registered substance abuse treatment program
- Part of a comprehensive package including:
  - prenatal care
  - chemical dependency counseling
  - family therapy
  - nutritional education
  - Other medical and psychosocial services
- Dosages are managed by addiction treatment specialists within registered methadone treatment programs

ACOG Committee Opinion No. 524, May 2012

Opioid-Maintenance Therapy During Pregnancy: Methadone

- Relationship between maternal methadone dosage and severity of NAS
  - Several studies have examined this relationship
  - Results are inconclusive and conflicting
  - Systematic literature review/meta-analysis concluded that the severity of neonatal abstinence syndrome does *not* appear to differ based on the maternal dose of methadone treatment

Dryden et al; BJOG 2001
Cleary et al; Addiction 2012
Seligman et al; J Peds 2010
Pizarro et al; Journal of Substance Abuse Treatment 40 (2011)
Cleary et al; Addiction 2010

Methadone treatment

- Well-recognized cause of QT prolongation in adults and can result in torsades de pointes
- The proposed mechanism for QT prolongation
  - Blockage of the potassium channel encoded by the human ether-a-go-go-related gene (hERG)
    - hERG was first identified in 1994 and is found on chromosome 7
    - codes for the potassium ion channel which mediates repolarization of the cardiac action potential
    - blockage of this channel results in prolongation of the QT interval and a propensity to arrhythmia

Parik et al; Arch Dis Child Fetal Neonatal Ed; 2011

Clinical Guidelines | 17 March 2009

QTc Interval Screening in Methadone Treatment FREE

Mori J. Krantz, MD; Judith Martin, MD; Barry Stimmel, MD; Davendra Mehta, MD; and Mark C.P. Haigney, MD

Ann Intern Med. 17 March 2009;150(6):387-395

***Table 2.* Consensus Recommendations**

Recommendation 1 (Disclosure): Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
Recommendation 2 (Clinical History): Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
Recommendation 3 (Screening): Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and then a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.
Recommendation 4 (Risk Stratification): If the QTc interval is greater than 450 ms but less than 500 ms, discuss potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
Recommendation 5 (Drug Interactions): Clinicians should be aware of interactions between methadone and other drugs that possess QT interval–prolonging properties or slow the elimination of methadone.

QTc = rate-corrected QT.

Maternal methadone therapy increases QTc interval in newborn infants

R Parikh,[1] T Hussain,[2] G Holder,[1] A Bhoyar,[3] AK Ewer[1, 4]

Arch Dis Child Fetal Neonatal Ed 2011;96:F141–F143.

- Methods:
  - 26 term infants born to mothers on methadone therapy had ECG recordings on days 1, 2, 4 and 7.
  - Results for days 1 and 2 were compared with healthy matched control infants born to mothers who were not receiving methadone
  - Results for days 4 and 7 were compared with published normal values
- Results:
  - In the methadone group, the QTc interval was significantly prolonged on days 1 and 2 of life
  - On days 4 and 7, this increase was no longer present
  - None of the infants in either group had any evidence of significant cardiac rhythm disturbance

Table 1 QTc interval in study patients

	N	Mean (ms)	SD (ms)	p Value
QTc interval day 1				
Methadone	26	435	34	<0.001
Control	26	401	29	
QTc interval day 2				
Methadone	24	433	36	<0.001
Control	26	390	28	
QTc interval day 4				
Methadone	26	392	33	0.83
Normal		400	20	
QTc interval day 7				
Methadone	25	378	25	0.99
Normal		400	20	

Arch Dis Child Fetal Neonatal Ed 2011;96:F141–F143. doi:10.1136/adc.2009.181701

Maternal methadone therapy increases QTc interval in newborn infants

R Parikh,[1] T Hussain,[2] G Holder,[1] A Bhoyar,[3] AK Ewer[1, 4]

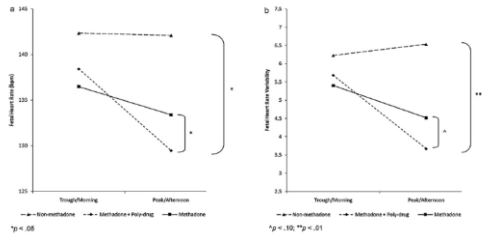
Arch Dis Child Fetal Neonatal Ed 2011;96:F141–F143.

- Conclusions:
  - Maternal methadone therapy can cause transient prolongation of the QTc interval in newborn infants in the first 2 days of life
  - Newborns exposed to methadone are at risk of cardiac rhythm disturbances
    - Bradycardia, tachycardia or an irregular heart rate in an infant born to a mother on methadone treatment should prompt investigation with a 12-lead ECG

Table 3
Planned one-way ANOVA contrasts between each group across both recordings.

	Fetal heart rate	Fetal heart rate variability	Motor activity
Trough/Morning			
Methadone + Poly-drug vs. Methadone	0.70	0.50	0.99
Methadone + Poly-drug vs. Non-Methadone	−1.22	−0.82	−1.22
Methadone vs. Non-Methadone	−1.89†	−1.29	−2.14*
Peak/Afternoon			
Methadone + Poly-drug vs. Methadone	−1.11	−1.45	1.38
Methadone + Poly-drug vs. Non-Methadone	−3.17**	−4.35***	−1.53
Methadone vs. Non-Methadone	−2.23*	−3.13**	−2.82**

† $p < .10$.
* $p < .05$.
** $p < .01$.
*** $p < .001$.



*p < .08 *p < .10; **p < .01

L.M. Jansson et al. / Drug and Alcohol Dependence 122 (2012) 213–219

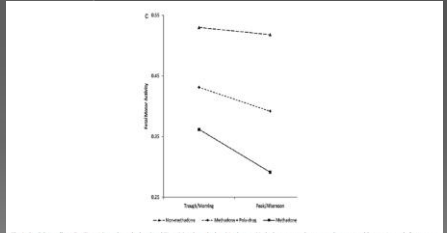


Fig. 1. Fetal data collected at Time 1 (trough methadone) and Time 2 (peak methadone) in the two Methadone-exposed groups and at comparable morning and afternoon times in the in Non-Methadone group. Notations refer to significance of differences in slope. (a) The Methadone + Poly-drug group showed significantly greater suppression in fetal heart rate (bpm) from Time 1 to Time 2 as compared to both the Non-Methadone and the Methadone-only groups. (b) The Methadone + Poly-drug group (MM + Poly) showed significantly greater suppression in fetal heart rate variability from Time 1 to Time 2 as compared to the Non-Methadone group (NM/A) and a trend level difference as compared to the Methadone only (MM/A) group in heart rate variability from Time 1 to Time 2. (c) Although there were significant differences at each recording between the Non-Methadone and Methadone + Poly drug groups (see Table 3), in fetal motor activity (i.e., the proportion of time engaged in motor activity during the 1-h recording), slopes did not differ over time.

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OBSTETRICS

Methadone and perinatal outcomes: a retrospective cohort study

Brian J. Cleary, MSc; Jean M. Donnelly, MB, BCh, BAO; Judith D. Strawbridge, MSc; Paul J. Gallagher, PhD; Tom Fahey, MD; Martin J. White, MD; Deirdre J. Murphy, MD

OBJECTIVE: The purpose of this study was to examine the relationship among methadone maintenance treatment, perinatal outcomes, and neonatal abstinence syndrome.

STUDY DESIGN: This was a retrospective cohort study of 61,030 singleton births at a large maternity hospital from 2000-2007.

RESULTS: There were 618 (1%) women on methadone at delivery. Methadone-exposed women were more likely to be younger, to book late for antenatal care, and to be smokers. Methadone exposure was associated with an increased risk of very preterm birth <32 weeks of gestation (adjusted odds ratio [aOR], 2.47; 95% confidence interval [CI], 1.40–4.34), being small for gestational age <10th percentile (aOR, 3.27; 95% CI, 2.49–4.28), admission to the neonatal unit (aOR, 9.14; 95% CI, 7.21–11.57), and diagnosis of a major congenital anomaly (aOR, 1.94; 95% CI, 1.10–3.43). There was a dose-response relationship between methadone and neonatal abstinence syndrome.

CONCLUSION: Methadone exposure is associated with an increased risk of adverse perinatal outcomes, even when known adverse sociodemographic factors have been accounted for. Methadone dose at delivery is 1 of the determinants of neonatal abstinence syndrome.

Key words: methadone, neonatal abstinence syndrome, perinatal outcome, pregnancy

Cite this article as: Cleary BJ, Donnelly JM, Strawbridge JD, et al. Methadone and perinatal outcomes: a retrospective cohort study. Am J Obstet Gynecol 2011;204:139.e1-9.

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TABLE 2
Maternal and perinatal outcomes by methadone exposure status

Variable	n	Exposed, n = 618 (1%)	Not exposed, n = 60,412 (99%)	Odds ratio	95% CI	Adjusted odds ratio*	95% CI
Mode of delivery	60,832						
Spontaneous vaginal		431 (69.8)	38,535 (64.0)	1	—	1	—
Elective lower segment cesarean section		40 (6.5)	4713 (7.8)	0.76	0.55–1.05	1.72	1.20–2.46
Emergency lower segment cesarean section		71 (11.5)	7496 (12.4)	0.85	0.66–1.09	1.26	0.94–1.68
Forceps/ventouse		75 (12.1)	9471 (15.7)	0.71	0.55–0.90	1.45	1.10–1.91
Meconium-stained liquor	60,533	76 (12.6)	9076 (15.1)	0.81	0.63–1.03	0.68	0.52–0.88
Preterm birth <37 wk	60,978	126 (20.4)	3382 (5.6)	4.32	3.54–5.27	2.47	1.97–3.11
Spontaneous preterm labor		93 (15.1)	2036 (3.4)	5.08	4.06–6.36	2.68	2.06–3.49
Very preterm birth <32 wk	60,978	27 (4.4)	727 (1.2)	3.75	2.53–5.56	2.27	1.40–3.69
Spontaneous preterm labor		22 (3.6)	363 (0.6)	6.11	3.94–9.47	2.99	1.69–5.29
Small for gestational age <10th percentile†	59,877	268 (45.9)	8379 (14.1)	5.15	4.37–6.07	2.21	1.85–2.64
Apgar score							
<3 at 1 min	60,725	20 (3.3)	636 (1.1)	3.18	2.02–5.00	1.94	1.12–3.37
<7 at 5 min	60,868	22 (3.6)	680 (1.1)	3.28	2.13–5.06	2.07	1.23–3.48
Ventilation required at resuscitation	60,977	6 (1.0)	398 (0.7)	1.48	0.66–3.32	0.92	0.33–2.55
Admitted to neonatal unit	61,029	329 (53.1)	8735 (14.5)	6.69	5.70–7.85	6.15	5.14–7.36
Congenital anomaly	61,029						
Any		47 (7.61)	1778 (2.94)	2.71	2.01–3.67	2.29	1.54–3.14
Minor		22 (3.56)	842 (1.39)	2.61	1.70–4.02	2.12	1.26–3.56
Major		19 (3.07)	647 (1.07)	2.92	1.84–4.65	1.94	1.10–3.43
Chromosomal		1 (0.16)	150 (0.25)	0.65	0.09–4.66	1.48	0.19–11.4
Unclassified		5 (0.81)	101 (0.17)	4.87	1.98–12.0	7.26	2.58–20.4
Perinatal death‡	61,030	15 (2.43)	491 (0.81)	3.04	1.80–5.11	1.70	0.87–3.30
Neonatal abstinence syndrome	61,029	267 (40.0)	39 (0.06)	1030	724–1466	426	289–728

RESEARCH www.AJOG.org

OBSTETRICS

Maternal treatment with opioid analgesics and risk for birth defects

Cheryl S. Broussard, PhD; Sonja A. Rasmussen, MD, MS; Jennita Reefhuis, PhD; Jan M. Friedman, MD, PhD; Michael W. Jann, PharmD; Tiffany Riehle-Colarusso, MD, MSE; Margaret A. Honein, PhD, MPH; for the National Birth Defects Prevention Study

OBJECTIVE: We examined whether maternal opioid treatment between 1 month before pregnancy and the first trimester was associated with birth defects.

STUDY DESIGN: The National Birth Defects Prevention Study (1997 through 2005) is an ongoing population-based case-control study. We estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for birth defects categories with at least 200 case infants or at least 4 exposed case infants.

RESULTS: Therapeutic opioid use was reported by 2.6% of 17,449 case mothers and 2.0% of 6701 control mothers. Treatment was statistically significantly associated with conoventricular septal defects (OR, 2.7; 95% CI, 1.1–6.3), atrioventricular septal defects (OR, 2.0; 95% CI, 1.2–3.6), hypoplastic left heart syndrome (OR, 2.4; 95% CI, 1.4–4.1), spina bifida (OR, 2.0; 95% CI, 1.3–3.2), or gastroschisis (OR, 1.8; 95% CI, 1.1–2.9) in infants.

CONCLUSION: Consistent with some previous investigations, our study shows an association between early pregnancy maternal opioid analgesic treatment and certain birth defects. This information should be considered by women and their physicians who are making treatment decisions during pregnancy.

Key words: analgesic, birth defect, medication, opioid, pregnancy

Cite this article as: Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314.e1-11.

Treatment Options for Opioid Dependence in Pregnancy: Buprenorphine

- May be used in pregnant patients under certain circumstances
- Consensus panel recommends buprenorphine be used only when physician believes potential benefits justify risks
- Potential candidates include
  - Women who are opioid addicted but cannot tolerate methadone
  - Those for whom program compliance has been difficult
  - Those who are adamant about avoiding methadone

Substance Abuse and Mental Health Services Administration 2011

Opioid-Maintenance Therapy During Pregnancy: Buprenorphine

- May be prescribed by trained and approved physicians in a medical office setting
  - Potentially increases the availability of treatment and decreases the stigma
- Patients need to be able to self-administer the drug safely and maintain adherence with their treatment regimen
- Compared with methadone clinics
  - the less stringent structure of buprenorphine treatment may make it inappropriate for some patients who require more intensive structure and supervision

Subutex versus Methdone ??

- Is one medication superior to the other in terms of:
  - Fetal assessment
  - NAS (severity)
    - Dosage of morphine and other withdrawal medications
    - Length of stay
    - Cost

Subutex and Methadone: Fetal effects

- Methadone-exposed fetuses between 32-35 weeks demonstrated greater motor activity suppression and shorter duration of movements than their buprenorphine-exposed counterparts
- Methadone has also demonstrated a significantly higher incidence of a non-reactive non-stress test for fetuses between 31-33 weeks compared to buprenorphine-exposed fetuses
- Growth restriction has been documented with both medications (Subutex and Methadone)

Jones et al; *Addiction* 2012

Neonatal Abstinence Syndrome (NAS)

Complex and poorly understood disorder

- Mainly referred to as:
  - constellation of signs and symptoms of opioid withdrawal that includes motor and tone problems, respiratory symptoms, gastrointestinal problems and central nervous system symptoms
- The syndrome itself is widely variable
  - different infants displaying different symptoms with different intensities over time

Jansson et al; *Acta Pædiatrica 2008*

Neonatal Abstinence Syndrome (NAS)

- Opiate withdrawal is often compounded by
  - Co-morbid poly-drug exposure
  - Maternal psychiatric medications
    - Antidepressants and benzodiazepines - also have their own withdrawal syndromes
- Neonatal abstinence syndrome withdrawal severity affects adaptation to postnatal life in critical regulatory areas of sleep, feeding, and autonomic function

Hayes et al; JAMA, May 9, 2012—Vol 307, No. 18

Neonatal Abstinence Syndrome (NAS)

- Varied clinical presentation likely due to
  - Specific opioid used
  - Maternal drug history
    - Smoking history
  - Timing of the most recent use of drug before delivery
  - Maternal metabolism
  - Maternal autonomic nervous system functioning
  - Net transfer of drug across the placenta
  - Placental metabolism
  - Infant metabolism and excretion
  - Other factors

Jansson et al; *Acta Pædiatrica 2008*
Hudak et al; Pediatrics 2012

Kuschel et al; *Arch. Dis. Child. Fetal Neonatal Ed.* 2004

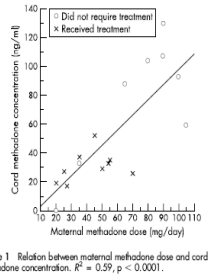


Figure 1 Relation between maternal methadone dose and cord methadone concentration. $R^2 = 0.59$, $p < 0.0001$.

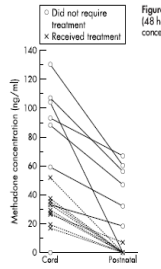


Figure 2 Cord and postnatal (48 hour) methadone concentrations.

Smoking and NAS

- Tobacco use in conjunction with methadone plays an important role in the timing and severity of NAS in prenatally exposed infants
  - Babies of mothers who reported smoking 20 or more cigarettes/day compared to smoking 10 or less cigarettes/day
    - Significantly higher NAS peak scores of 9.8 versus 4.8
    - Altered timing of peak NAS scores (113.0 h versus 37.8 h)
      - Choo et al, Drug and Alcohol Dependence 2004
- Past 30-day daily average number of cigarettes smoked was significantly positively associated with
  - total amount of morphine (mg) needed to treat neonatal abstinence syndrome (NAS)
  - number of days medicated for NAS
  - neonatal length of hospital stay in days
  - negatively associated with 1 and 5 minute Apgar scores

Jones et al ; Drug and Alcohol Dependence 2012

Neonatal Abstinence Syndrome (NAS)

TABLE 3 Clinical Features of the Neonatal Narcotic Abstinence Syndrome

Neurologic Excitability	Gastrointestinal Dysfunction
Tremors	Poor feeding
Irritability	Uncoordinated and constant sucking
Increased wakefulness	Vomiting
High-pitched crying	Diarrhea
Increased muscle tone	Dehydration
Hyperactive deep tendon reflexes	Poor wt gain
Exaggerated Moro reflex	Autonomic signs
Seizures	Increased sweating
Frequent yawning and sneezing	Nasal stuffiness
	Fever
	Mottling
	Temperature instability

Neonatal Abstinence Syndrome (NAS)

Preterm infants

- Lower risk of drug withdrawal with less severe and/or prolonged courses
- Lower gestational age seems to correlate with a lower risk of neonatal withdrawal
- The apparent decreased severity of signs in preterm infants may relate to
  - developmental immaturity of the CNS
  - differences in total drug exposure
  - lower fat depots of drug

Hudak et al; Pediatrics 2012

Neonatal Abstinence Syndrome (NAS)

Preterm infants

- Use Caution!!
  - The clinical evaluation of the severity of abstinence may be more difficult in preterm infants
  - No specific scoring tools have been developed for available for preterm babies

Hudak et al; Pediatrics 2012

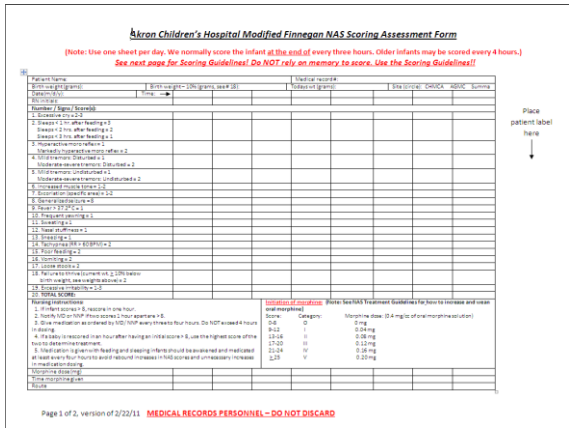
Neonatal Abstinence Syndrome (NAS): Assessment

Optimal evaluation for the affected infants is currently unknown
- Due to overall poor understanding of NAS

- Several scoring scales have been developed for NAS
  - Purpose to allow a systematic, objective, periodic and thorough evaluation of the newborn to determine the course of the syndrome and the need for pharmacologic therapy

- Many institutions use modified scales, and there are no standardized parameters for scoring individual items.

Jansson et al; *Acta Pædiatrica 2008*



Akron Children's Hospital Modified Finnegan NAS Scoring Assessment Form

(Note: Use one sheet per day. We normally score the infant at the end of every three hours. Older infants may be scored every 4 hours.)

See next page for Scoring Guidelines! Do NOT rely on memory to score. Use the Scoring Guidelines!!

Patient Name | Medical record# | Birth weight (grams) | Birth weight – 10%/grams, see # (§) | Delivery (V/c) | Time: → | Wt today | Number / Signs / Score(s) | 1. Excessive cry x 2 | 2. Sleeps < 1 hr. after feeding = 3; Sleeps < 2 hrs. after feeding = 2; Sleeps < 3 hrs. after feeding = 1 | 3. Hyperactive moro reflex = 1; Markedly hyperactive moro reflex = 2 | 4. Mild tremors: Disturbed = 1; Moderate-severe tremors: Disturbed = 2 | 5. Mild tremors: Undisturbed = 1; Moderate-severe tremors: Undisturbed = 2 | 6. Increased muscle tone = 2 | 7. Excoriation (specify area) = 1-2 | 8. Generalized rash/acne = 1 | 9. Fever > 37.2°C = 1 | 10. Frequent yawning = 1 | 11. Sweating = 1 | 12. Nasal stuffiness = 1 | 13. Sneezing = 1 | 14. Tachypnea (RR > 60/min) = 2 | 15. Poor feeding = 2 | 16. Vomiting = 2 | 17. Loose stools = 2 | 18. Failure to thrive (current wt. ↓ 10% below birth weight, see weights above) = 2 | 19. Excessive irritability = 1-3 | 20. TOTAL SCORE: | Nursing Instructions: 1. If infant scores > 8, rescore in one hour. 2. Notify MD or NNP if total score ≥ 1 hour apart are > 8. 3. Give medication as ordered by MD / NNP every three to four hours. Do NOT exceed 4 hours in dosing. 4. If a baby is rescored in an hour after having an initial score > 8, use the highest score of the two to determine treatment. 5. Medication is given with feeding and sleeping infants should be awakened and medicated at least every four hours to avoid rebound increases in NAS scores and unnecessary increases in medication dosing. | Initiation of morphine: (Refer to NAS Treatment Guidelines for how to increase and wean oral morphine)

Score:	Category:	Morphine dose: (0.4 mg/cc of oral morphine solution)
0-8	0	0 mg
9-12	I	0.04 mg
13-16	II	0.08 mg
17-20	III	0.12 mg
21-24	IV	0.16 mg
≥ 25	V	0.20 mg

Morphine dosing | Time morphine given | Route

Place patient label here

Page 1 of 2, version of 2/22/11 **MEDICAL RECORDS PERSONNEL – DO NOT DISCARD**

TABLE 4. Neonatal Drug-Withdrawal Scoring System

Signs	Score			
	0	1	2	3
Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate or marked increase when undisturbed; subside when fed or held snugly	Marked increase or continuous even when undisturbed, going on to seizure-like movements
Irritability (excessive crying)	None	Slightly increased	Moderate to severe when disturbed or hungry	Marked even when undisturbed
Reflexes	Normal	Increased	Markedly increased	
Stools	Normal	Explosive, but normal frequency	Explosive, more than 8 d	
Muscle tone	Normal	Increased	Rigidity	
Skin abrasions	No	Redness of knees and elbows	Breaking of the skin	
Respiratory rate/minute	<55	55–75	76–95	
Repetitive sneezing	No	Yes		
Repetitive yawning	No	Yes		
Vomiting	No	Yes		
Fever	No	Yes		

Reprinted with permission from Lipsitz PJ. *Clin Pediatr.* 1975;14:592–594.

Neonatal Abstinence Syndrome (NAS)

- The scoring thresholds and time between scores for institution of pharmacotherapy vary considerably

- Standardization of evaluation is necessary for the provision of optimal pharmacotherapy as well as the comparative interpretation of research findings

Jansson et al; *Acta Pædiatrica 2008*

Sarkar et al; *Journal of Perinatology* (2006)

National survey sent to determine monitoring and treatment of NAS

- Of the 102 individuals contacted, 75 participated in the survey
  - Only 41 of the respondents (54.5%) had a written policy regarding the management of neonatal NAS
  - 53 respondents (70%) always use an abstinence scoring system to determine when to start, titrate, or terminate pharmacologic treatment of neonatal NAS
  - Finnegan scoring method was the most commonly used abstinence scoring system (49 of 75, 65%)
  - 3 Respondents used the Lipsitz tool

Subutex versus Methdone ??

- Is one medication superior to the other in terms of:
  - NAS (severity)
    - Dosage of morphine and other withdrawal medications
  - Length of stay
  - Cost

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O'Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

- Double-blind, double-dummy, flexible-dosing, randomized, controlled study in which buprenorphine and methadone were compared for use in the comprehensive care of 175 pregnant women with opioid dependency at eight international sites
- Primary outcomes
  - Number of neonates requiring treatment for NAS
  - The peak NAS score
  - The total amount of morphine needed to treat NAS
  - The length of the hospital stay for neonates
  - Neonatal head circumference

Jones et al; *NEJM* 2012

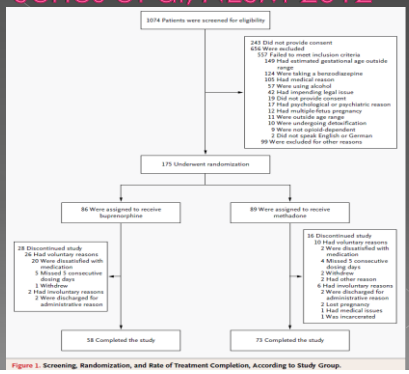


Figure 1. Screening, Randomization, and Rate of Treatment Completion, According to Study Group.

Jones et al; *NEJM*; December 2010

Table 2. Primary and Secondary Outcomes in the Methadone and Buprenorphine Groups.*

Outcome	Methadone (N=73)	Buprenorphine (N=58)	Odds Ratio (95% CI)	P Value
Primary outcomes				
Treated for NAS — no. (%)	41 (57)	27 (47)	0.7 (0.2–1.8)	0.26
NAS peak score	12.8±0.6	11.0±0.6		0.04
Total amount of morphine for NAS — mg	10.4±2.6	1.1±0.7		<0.0091†
Duration of infant's hospital stay — days	17.5±1.5	10.0±1.2		<0.0091†
Infant's head circumference — cm	33.0±0.3	33.8±0.3		0.03
Secondary neonatal outcomes				
Duration of treatment for NAS — days	9.9±1.6	4.1±1.0		<0.003125†
Weight at birth — g	2878.5±66.3	3093.7±72.6		0.03
Length at birth — cm	47.8±0.5	49.8±0.5		0.005
Preterm, <37 wk — no. (%)	14 (19)	4 (7)	0.3 (0.1–2.0)	0.07
Gestational age at delivery — wk	37.9±0.3	39.1±0.3		0.007
Apgar score				
1 min	8.0±0.2	8.1±0.2		0.87
5 min	9.0±0.1	9.0±0.1		0.69
Secondary maternal outcomes				
Cesarean section — no. (%)	27 (37)	17 (29)	0.6 (0.2–2.0)	0.23
Maternal weight gain — kg	8.6±1.0	8.3±0.9		0.80
Abnormal fetal presentation during delivery — no. (%)	10 (14)	3 (5)	0.3 (0.0–2.4)	0.09
Analgesia during delivery — no. (%)	60 (82)	49 (85)	1.1 (0.3–4.8)	0.85
Positive drug screen at delivery — no. (%)	11 (15)	5 (9)	0.5 (0.1–2.7)	0.27
Medical complications at delivery — no. (%)	37 (51)	18 (31)	0.5 (0.2–0.9)	0.03
Did not complete study — no. (%)	16 (18)	28 (33)	2.6 (1.3–5.6)	0.02
Amount of voucher money earned for drug-negative tests — U.S. $	1,570.00±121.72	1,391.39±123.59		0.31
No. of prenatal obstetrical visits	8.8±0.5	8.7±0.4		0.86

Jones et al; *NEJM*; December 2010

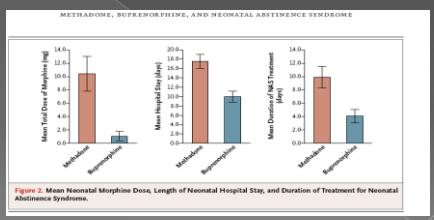


Figure 2. Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome.

Jones et al; *NEJM*; December 2010

Conclusions

- The results support the use of buprenorphine as a potential first-line medication for pregnant opioid-dependent women who are new to treatment
  - Important to understand that buprenorphine will not be effective for all patients
  - With the newer data available, the indications for the use of buprenorphine are in-flux currently
- Current trend seems to be in favor of using buprenorphine
  - The potential risk of unrecognized adverse long-term outcomes, which is inherent in the widespread use of relatively new medications during pregnancy, should always be taken into consideration

ACOG Committee Opinion No. 524, May 2012

Opioid-Maintenance Therapy During Pregnancy: Buprenorphine

- Disadvantages when compared with methadone
  - reports of hepatic dysfunction
  - the lack of any long-term data on infant and child effects
  - a clinically important patient dropout rate due to dissatisfaction with the drug
  - a more difficult induction with the potential risk of precipitated withdrawal
  - increased risk of diversion (ie, sharing or sale) of prescribed buprenorphine


Addiction
RESEARCH REPORT

Differences in the profile of neonatal abstinence syndrome signs in methadone- versus buprenorphine-exposed neonates

Diann E. Gaalema[1], Teresa Linares Scott[2], Sarah H. Heil[2,3], Mara G. Coyle[3], Karol Kaltenbach[4], Gary J. Badger[2], Amelia M. Arria[4], Susan M. Stine[3], Peter R. Martin[5] & Hendrée E. Jones[4,5]

Table 2 Number (%) of neonates who ever had a score >0.

NAS sign	Methadone (n = 72)	Buprenorphine (n = 57)	χ^2 P-value
Total score	72 (100)	57 (100)	1.00
Disturbed tremors	72 (100)	55 (96)	0.11
Increased muscle tone	71 (99)	57 (100)	0.37
Sleep	65 (90)	55 (96)	0.17
Tachypnea	62 (86)	51 (89)	0.57
Fever	61 (85)	53 (93)	0.15
Undisturbed tremors	58 (81)	36 (63)	0.03
Hyperactive Moro reflex	55 (76)	33 (58)	0.03
Sneezing	55 (76)	53 (93)	0.01
Crying	40 (56)	32 (56)	0.94
Excessive irritability	39 (54)	38 (67)	0.15
Poor feeding	39 (54)	28 (49)	0.57
Vomiting	38 (53)	33 (58)	0.56
Excoriation	34 (47)	32 (56)	0.31
Loose stools	33 (46)	40 (70)	0.01
Nasal stuffiness	20 (28)	29 (51)	0.01
Frequent yawning	15 (21)	17 (30)	0.24
Sweating	15 (21)	12 (21)	0.98
Failure to thrive	12 (17)	7 (12)	0.49
Generalized seizure	0	2 (4)	0.11

Entries shown in bold type indicate significant differences between medication conditions. NAS = neonatal abstinence syndrome.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- There was a significant difference in the median time of morphine treatment initiation among the treated infants
- Median time to treatment initiation
  - methadone- exposed
    - 36 (26–60) hours
  - buprenorphine-exposed
    - 59 (46–83) hours ($P < 0.01$)

NAS Assessment/Treatment

- Initial treatment should be supportive care (non-pharmacological approach
  - There is sparse empirical literature regarding the non-pharmacologic care of drug exposed neonates
- Pharmacologic therapy may not be needed and will prolong hospitalization
- The individual functioning of each infant should be assessed thoroughly
  - Evaluating the ability to regulate sleep/awake states, autonomic, sensory, motor, and interactive capacities; and displayed behaviors

Kassim et al; *Current Paediatrics* (2006) 16, 172–175

NAS: Assessment/Treatment

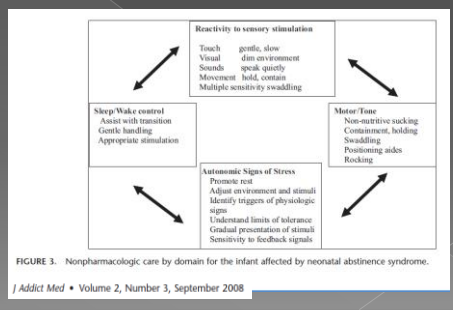


FIGURE 3. Nonpharmacologic care by domain for the infant affected by neonatal abstinence syndrome.

J Addict Med • Volume 2, Number 3, September 2008

NAS: Assessment/Treatment

Mother-Infant Dyad

- Commonly "out of sync" or "not bonding"
  - Due to often multiple negative experiences and maladaptive behaviors of the mother
  - Due to the frequently confusing constellation of signs/symptoms of abstinence and neurobehavioral dysregulation of the infant
- Requires a caring and well-trained staff which focuses on providing ongoing parenting support and education
  - Getting mother /parents involved with therapy and nursing to learn specific soothing methods for their baby, cueing and sleep schedules
    - Can result in improved maternal satisfaction and confidence
  - Single patient rooms if available to enable improved bonding

Janson et al; Neoreviews 2011

Breastfeeding

- Minimal levels of methadone and buprenorphine are found in breast milk regardless of the maternal dose
- Breastfeeding should be encouraged in patients without HIV who are not using additional drugs and who have no other contraindications

Hudak et al; Pediatrics 2012

NAS Treatment

- For infants with significant NAS symptoms pharmacotherapy is warranted
- Medications used to treat the neurobehavioral symptoms related to prenatal exposure to psychoactive drugs vary widely among institutions

Sarkar et al; *Journal of Perinatology* (2006)

Table 1 Drugs used in the management of neonatal psychomotor behavior consistent with withdrawal following *in utero* opioid or polydrug exposure

Opioid withdrawal		*Polydrug withdrawal*	
Drugs used as first line of management (Number of respondents)	Drugs added as second line of management (Number of respondents)	Drugs used as first line of management (Number of respondents)	Drugs added as second line of management (Number of respondents)
Opioids (67, 63%)	Phenobarbital (24) Intravenous morphine (10) Methadone (8) Clonidine (3) Diazepam (2)	Opioids (59, 52%)	Phenobarbital (27) Methadone (3) Clonidine (2) Diazepam (1) Variable (6)
Methadone (15, 20%)	Oral morphine (6) Phenobarbital (4) Tincture of opium (3) Clonidine (2)	Phenobarbital (24, 32%)	Opioids (8) Diazepam (8) Methadone (4) Rarely seen (4)
Phenobarbital (13, 17.3%)	Oral morphine (4) Methadone (4) Tincture of opium (3) Diazepam (2)	Methadone (8, 10.6%)	Phenobarbital (4) Opioids (3) Diazepam (1)
		Rarely seen (4, 5.4%)	

NAS Treatment

- Opioids
  - Drug of choice for neonatal opioid withdrawal
  - Most commonly used first-line medications for opioid withdrawal
    - oral morphine solution
    - tincture of opium
    - Methadone

Janson et al; Peds in review 2011
Osborn et al; The Cochrane Collaboration 2010

NAS Treatment

- For polydrug exposed infants, commonly employed medications are opioids, phenobarbital, and methadone
- Weight-based versus symptom-based treatment strategies can be employed

Janson et al; Peds in review 2011
Osborn et al; The Cochrane Collaboration 2010

NAS Treatment

- Little empirically based evidence supports the use of one medication or one treatment strategy over the other
  - reflecting a paucity of randomized studies in this area
- Newer agents for the treatment of NAS are being explored
  - clonidine
  - buprenorphine

Janson et al; Peds in review 2011

NAS Research

- State Project
- Local Projects
- MFM Quip/NICU QUIP
- Vermont-Oxford iNICU

JOHN R. KASICH
GOVERNOR • STATE OF OHIO
Communication Department

Supporting Life-Saving Research at Ohio's Children's Hospitals

Last July, Governor John R. Kasich visited Nationwide Children's Hospital in Columbus, at which time he visited with doctors and researchers and pledged $2 million in state funds to Ohio's children's hospitals for collaborative research innovations. The governor's commitment will provide $1 million each for the following research projects:

Asthma Research:

- Asthma is one of the leading causes of avoidable hospital admissions for children. This initiative will help hospitals collect and share consistent data on asthma assessments and treatments, improving care and curbing unnecessary health-care costs. The research is highly innovative, harnessing the collective expertise and resources of children's hospitals across the state.
- Ohio's children's hospitals will build a comprehensive data warehouse that links clinical, demographic and other health-outcomes data with biological markers for children with asthma who obtain care at children's hospitals.
- Ohio's children's hospitals will compare and understand effectiveness of strategies currently utilized for the treatment of acute asthma and will better define and anticipate treatment response based on the new data infrastructure.

Neonatal Abstinence Syndrome (NAS) Research:

- This groundbreaking research on NAS, commonly referred to as "drug addicted babies," is relevant and timely due to the unfortunate, growing trend of opiate and other substance abuse. Preliminary research suggests that in 2011 alone, 606 babies were born with NAS and treated in Ohio's children's hospitals.
- This research aligns with other statewide efforts to end the cycle of drug misuse and abuse. This project will provide essential baseline data on NAS and ensure better outcomes at less cost for mothers and babies.
- Ohio's children's hospitals will conduct retrospective analyses at each hospital in 2011 and prospective evaluation in 2012 for types of drug exposures and co-exposures in babies in Ohio. Ohio's children's hospitals will document current treatment plans to better understand them and look to standardize treatment associated with the best outcomes, fewest side effects and shortest duration of withdrawal for babies with NAS.
  - Ohio's children's hospitals will assess (for babies): demographic characteristics of babies born with NAS; regional patterns in usage and outcomes of treatment; differences in the drugs of abuse detected; lengths of hospital stay; recidivism for these babies; and incidence of multiple exposures.
  - Ohio's children's hospitals will assess (for mothers): demographic characteristics of using mothers; regional patterns in usage; degree to which management of the addicted mother during pregnancy impacts the severity of NAS and impacts on the baby; and estimated differences in outcomes of mothers based on the treatment options.

Ohio's children's hospitals will partner with Ohio Medicaid to capture Medicaid costs for both research efforts over the next two years and document improvements in outcomes.

Funds for both projects are from the Children's Health Insurance Program Reauthorization Act performance bonus Ohio received for enrolling more eligible children in Medicaid and CHIP.

SURVEY OF INCIDENCE AND OUTCOMES OF CHILDREN WITH NEONATAL ABSTINENCE SYNDROME

The Ohio Children's Hospitals Neonatal Research Consortium

- Objectives/Study Design
  - Conduct prospective epidemiologic evaluation of the scope of NAS in the state of Ohio over calendar year 2012
  - Information will be collected in a uniform manner from all sites participating in the research consortium
    - Rainbow Babies and Children's Hospital
    - Akron Children's Hospital Medical Center
    - Toledo Children's Hospital
    - Dayton Children's Hospital
    - Nationwide Children's Hospital
    - Cincinnati Children's Hospital
  - In addition, evaluation of a subset of clinically ordered samples (urine and meconium) and discarded tissue (umbilical cord specimens) will be collected and analyzed for presence of illicit drugs and for metabolites

SURVEY OF INCIDENCE AND OUTCOMES OF CHILDREN WITH NEONATAL ABSTINENCE SYNDROME

The Ohio Children's Hospitals Neonatal Research Consortium

- Aim 1: To describe differences between children's hospitals in Ohio and the demographic characteristics of neonates with abstinence syndrome, differences in the drugs of abuse detected, differences in management protocols for babies with NAS, differences in lengths of stay, and recidivism
- Aim 2: To measure the substances and frequency of NAS in infants known to be exposed to maternal narcotics to detect regional patterns, and the incidence of multiple exposures.
  - Utilize the USDTL cord-stat method to assay 13 common drugs of abuse including
    - amphetamines, cannabinoids, cocaine, PCP, opiates, methadone, tramadol, oxycodone, meperidine, buprenorphine, propoxyphene, barbiturates, benzodiazepines

SURVEY OF INCIDENCE AND OUTCOMES OF CHILDREN WITH NEONATAL ABSTINENCE SYNDROME

The Ohio Children's Hospitals Neonatal Research Consortium

- Aim 3: To compare the performance of assays of the urine, meconium and umbilical cord in a subset of 100 infants to determine the sensitivity, timeliness, and costs of each source
- Aim 4: To estimate the degree to which management of the addicted mother during pregnancy impacts the severity of NAS
- Aim 5: To estimate differences in outcome according to the severity of the NAS, and to the medications (opioids and phenobarbital) used to manage NAS

Local Neonatal Abstinence Project

- Aim
  - To reduce the length of stay (LOS) for babies ≥ 35 weeks gestation at birth born with neonatal narcotic abstinence syndrome by 20%
- Goals
  - Adopt the Johns Hopkins modified Finnegan scoring tool and oral narcotic dosing regimen
  - Staff Training
  - Assure a high rate (>80%) compliance with use
  - Assess ***balancing measures***
    - Readmission to hospital within 1 week of DC
    - Occurrence of seizures increases
  - Assess ***outcome measures***
    - Length of stay
    - Cost changes
  - Assess ***process measures*** for compliance, consistency of use and satisfaction
  - Adopt a Family Centered approach

Akron Children's Hospital Modified Finnegan NAS Scoring Assessment Form

(Note: Use one sheet per day. We normally score the infant at the end of every three hours. Older infants may be scored every 4 hours.)
See next page for Scoring Guidelines! Do NOT rely on memory to score. Use the Scoring Guidelines!!

Patient Name: | Medical record#:
Birth weight (grams): | Birth weight – 10% (grams, see # 18): | Today's wt (grams): | Site (circle): CHUCA ADUC Summa
Delay in (hr): | Time: →

Number / Signs / Score(s):								
1. Excessive cry = 2								
2. Sleeps < 1 hr. after feeding = 3 Sleeps < 2 hrs. after feeding = 2 Sleeps < 3 hrs. after feeding = 1								
3. Hyperactive moro reflex = 1 Markedly hyperactive moro reflex = 2								
4. Mild tremors: Disturbed = 1 Moderate-severe tremors: Disturbed = 2								
5. Mild tremors: Undisturbed = 1 Moderate-severe tremors: Undisturbed = 2								
6. Increased muscle tone = 2								
7. Excoriation (specify area) = 2								
8. Generalized seizure = 5								
9. Fever > 37.2°C = 1								
10. Frequent yawning = 2								
11. Sweating = 1								
12. Nasal stuffiness = 1								
13. Sneezing = 1								
14. Tachypnea (RR > 60/PUR) = 2								
15. Poor feeding = 2								
16. Vomiting = 2								
17. Loose stools = 2								
18. Failure to thrive (current wt. ≥ 10% below birth weight, see weights above) = 2								
19. Excessive irritability = 2-3								
20. TOTAL SCORE:								

Nursing instructions:
1. If infant scores ≥ 8, rescore in one hour.
2. Notify MD or NNP if now scores 1 hour apart are ≥ 8.
3. Give medication as ordered by MD/NNP every three to four hours. Do NOT exceed 4 hours in dosing.
4. If baby is rescored in an hour after having an initial score ≥ 8, use the highest score of the two to determine treatment.
5. Medication is given with feeding and sleeping infants should be evaluated and medicated at least every four hours to avoid rebound increases in NAS scores and unnecessary increase in medication dosing.

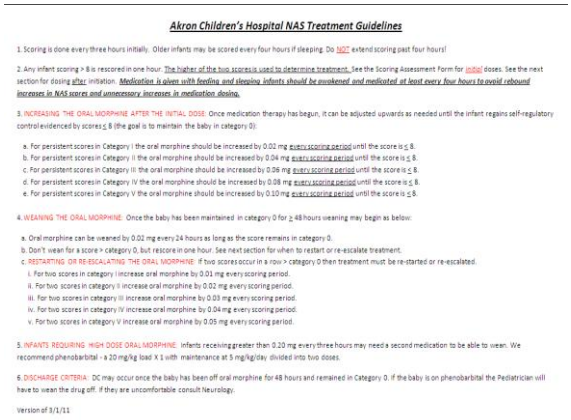
Initiation of morphine (Note: See NAS Treatment Guidelines for how to increase and wean oral morphine)

Score:	Category:	Morphine dose: (0.4 mg/cc of oral morphine solution)
0-8	I	0 mg
9-12	II	0.04 mg
13-16	III	0.08 mg
17-20	IV	0.12 mg
21-24	IV	0.16 mg
≥ 25	V	0.20 mg

Morphine dose (mg):
Time morphine given:
Route:

Place patient label here

Page 1 of 2, version of 2/22/11 **MEDICAL RECORDS PERSONNEL – DO NOT DISCARD**



Akron Children's Hospital NAS Treatment Guidelines

1. Scoring is done every three hours initially. Older infants may be scored every four hours if sleeping. Do NOT extend scoring past four hours!

2. Any infant scoring > 8 is rescored in one hour. The higher of the two scores is used to determine treatment. See the Scoring Assessment Form for initial doses. See the next section for dosing after initiation. ***Medication is given with feeding, and sleeping infants should be awakened and medicated at least every four hours to avoid rebound increases in NAS scores and unnecessary increases in medication dosing.***

3. INCREASING THE ORAL MORPHINE AFTER THE INITIAL DOSE: Once medication therapy has begun, it can be adjusted upwards as needed until the infant regains self-regulatory control evidenced by scores ≤ 8 (the goal is to maintain the baby in category 0):

a. For persistent scores in Category I the oral morphine should be increased by 0.02 mg every scoring period until the score is ≤ 8.
b. For persistent scores in Category II the oral morphine should be increased by 0.04 mg every scoring period until the score is ≤ 8.
c. For persistent scores in Category III the oral morphine should be increased by 0.06 mg every scoring period until the score is ≤ 8.
d. For persistent scores in Category IV the oral morphine should be increased by 0.08 mg every scoring period until the score is ≤ 8.
e. For persistent scores in Category V the oral morphine should be increased by 0.10 mg every scoring period until the score is ≤ 8.

4. WEANING THE ORAL MORPHINE: Once the baby has been maintained in category 0 for ≥ 48 hours weaning may begin as below:

a. Oral morphine can be weaned by 0.02 mg every 24 hours as long as the score remains in category 0.
b. Don't wean for a score > category 0, but rescore in one hour. See next section for when to restart or re-escalate treatment.
c. RESTARTING OR RE-ESCALATING THE ORAL MORPHINE: If two scores occur in a row > category 0 then treatment must be re-started or re-escalated.
i. For two scores in category I increase oral morphine by 0.01 mg every scoring period.
ii. For two scores in category II increase oral morphine by 0.02 mg every scoring period.
iii. For two scores in category III increase oral morphine by 0.03 mg every scoring period.
iv. For two scores in category IV increase oral morphine by 0.04 mg every scoring period.
v. For two scores in category V increase oral morphine by 0.05 mg every scoring period.

5. INFANTS REQUIRING HIGH DOSE ORAL MORPHINE: Infants receiving greater than 0.20 mg every three hours may need a second medication to be able to wean. We recommend phenobarbital - a 20 mg/kg load X 1 with maintenance at 5 mg/kg/day divided into two doses.

6. DISCHARGE CRITERIA: DC may occur once the baby has been off oral morphine for 48 hours and remained in Category 0. If the baby is on phenobarbital the Pediatrician will have to wean the drug off. If they are uncomfortable consult Neurology.

Version of 3/1/11

Local Neonatal Abstinence Project

Pre-data (Coyle Protocol)

- Total 89 babies
- Summa
  - 53 total
    - 8 no treatment required
    - 37 compliant when treatment required
- General
  - 17 total
    - 2 no treatment required
    - 12 compliant when treatment required
- Main Campus
  - 19 total
    - 2 no treatment required
    - 11 compliant when treatment required

Post Data (Johns Hopkins Protocol)

- Total 77 babies
- Summa
  - 30 total
    - 17 no treatment required
    - 4 compliant with treatment
- General
  - 27 total
    - 4 no treatment required
    - 16 compliant with treatment
- ACH Main Campus
  - 20 total
    - 3 no treatment required
    - 7 compliant with treatment

Conclusions

- Increasing opiate use in pregnancy (and in the general population) has become an major public health problem
  - Associated morbidities and costs
  - The majority of these mothers are also smokers which increases risks further
- Although not FDA approved for opiate maintenance in pregnancy, buprenorphine appears to have several benefits compared to methadone in terms of NAS severity and LOS
  - Concerns regarding a higher drop-out rate around induction-time needs to be investigated
  - Long-term safety profiles remain unknown with buprenorphine

Conclusions

- There appears to be an association between birth defects and in-utero opioid exposure in general
  - More research in this area is needed
- More collaboration at the state/nation-wide level will be needed to foster more improved, uniform evaluation and future treatment strategies
- More randomized, prospective studies are needed to help determine the best maternal and neonatal treatment strategies

Questions?

- Thank you