

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

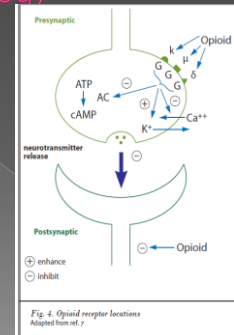
Table 1. Analgesic effects at opioid receptors.

	Mu (μ)	Delta (δ)	Kappa (κ)
	<ul style="list-style-type: none"> • Mu 1 - Analgesia • Mu 2 - Sedation, vomiting, respiratory depression, pruritis, euphoria, anorexia, urinary retention, physical dependence 	<ul style="list-style-type: none"> • Analgesia, spinal analgesia 	<ul style="list-style-type: none"> • 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

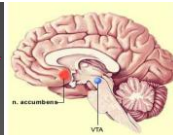


Trescot et al; Pain Physician 2008

Opioids: Pharmacology

Opioids and endogenous opioids

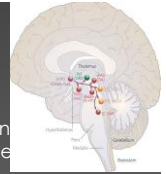
- Activate presynaptic receptors on GABA neurons
 - Inhibits the release of GABA in the ventral tegmental area
 - Allows dopaminergic neurons to fire more vigorously
 - Extra dopamine in the nucleus accumbens is intensely pleasurable
 - Dopamine seems to strengthen the inherent rewarding characteristics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

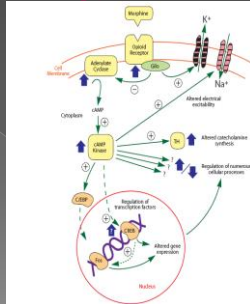
Opioids: Pharmacology

- Opioid withdrawal syndrome
 - Thought to be due to hyperactivity in the locus coeruleus once opiate inhibition is discontinued
 - $\alpha 2$ -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 used 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. DEA schedule 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, meperidine, butorphanol, pentazocine, propoxyphene
V	Medical use; low abuse potential	Buprenex, Phenergan with codeine

Modified from ref. 10

5138

www.painphysicianjournal.com

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

- 4:1 ratio 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®

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

Hong K. Kim, Monica Soudky, 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

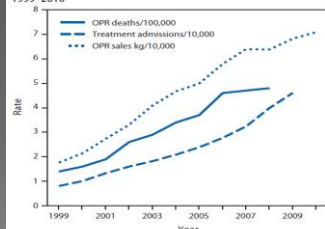
Epidemiology

- 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

FIGURE 2. Rates* of opioid pain reliever (OPR) overdose death, OPR treatment admissions, and kilograms of OPR sold — United States, 1999–2010



* Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold

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*

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

DEI, dextroamphetamine; DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; MDA, methylendioxyamphetamine; MDEA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxyamphetamine (ecstasy); and MDEA, 3-methoxy-4-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

Winklerbauret et al; Euro Addict Research 2009

RESIDENTS' PAPERS

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Universal screening for substance abuse at the time of parturition

Ali Azadi, MD; Gary A. Diddy 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. Diddy 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

RESIDENTS' PAPERS

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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

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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, 2000-2009JAMA, May 9, 2012—Vol 307, No. 18
Corrected on May 16, 2012

Stephen W. Patrick, MD, MPH, MS

Robert E. Schumacher, MD

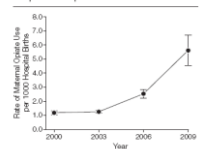
Brian D. Benneyworth, MD, MS

Elizabeth E. Krans, MD, MS

Jennifer M. McAllister, MD

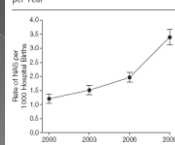
Matthew M. Davis, MD, MAPP

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 antenatal opiate use are 967 and 833 494 in 2000; 1058 and 849 133 in 2003; 1160 and 879 910 in 2006; and 4563 and 816 554 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 2200 and 784 191 in 2000; 3761 and 890 582 in 2003; 5200 and 1000 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 (\$3 400-45 400)	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 (6000-7300)	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

Year	Unweighted Sample, No.	Weighted % (95% CI)			
		Medicaid	Private Payer	Self-pay	Other Payer
2000	2920	68.7 (63.9-76.7)	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 (4.5-8.3)	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)	17.5 (15.1-20.4)	2.9 (2.4-3.4)	2.0 (1.4-2.9)

^aPercentage may not sum to 100 because of rounding.1938 JAMA, May 9, 2012—Vol 307, No. 18
Corrected on May 16, 2012

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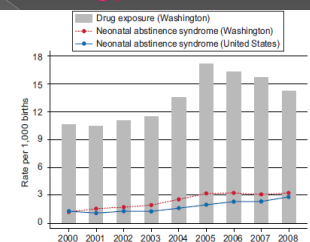
Creanga et al; Obstetrics and
Gynecology 2012

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

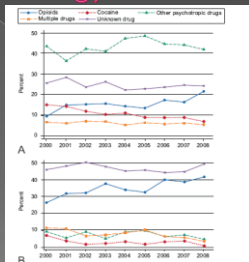


Fig. 2. Contribution of specific categories of drugs to prenatal drug exposure (A) and neonatal abstinence syndrome (B) in Washington State 2000-2008. Note: Exclusive exposure to opioids, cocaine, and other psychotropic drugs is shown; exposure to multiple drugs includes exposure to two or more drug 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	Drug-Unexposed (n=660,451) Mean (SD) or %	Mean (SD) or %	Drug-Exposed (n=9,824)		
			Crude OR (95% CI) ^a	LBW-Adjusted OR (95% CI) ^b	Prematurity-Adjusted OR (95% CI) ^c
Delivery-related associations					
Cesarean delivery	28.1	31.0	1.2 (1.0-1.3)		
Preterm delivery ^d	8.4	21.1	3.0 (2.8-3.1)		
Birth weight (g) ^d	3,185.9 (567.5)	3,062.6 (650.1)	-326.9 (-318.7 to -315.1)		
LBW ^e	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.

^a Unadjusted model.

^b Model adjusted only for LBW (birthweight data missing for 0.3% of cases).

^c 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 Pediatr 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

Parikh 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(3):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,³ A Bhoyar,³ AK Ewer^{1, 4}

Arch Dis Child Fetal Neonatal Ed 2011;96:F143-F145

• 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 (sec)	SD (sec)	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:F143-F145. 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 Bhojra,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

218

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

Table 3

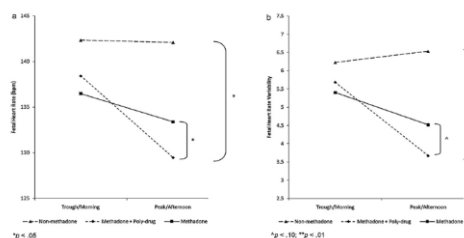
Planned one-way ANOVA contrasts between each group across both recordings.

	Fetal heart rate	Fetal heart rate variability	Motor activity
Through/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*	−4.39**	−1.53
Methadone vs. Non-Methadone	−2.23*	−3.13*	−2.82*

* $p < .05$.

** $p < .01$.

*** $p < .001$.



* $p < .05$

** $p < .01$, *** $p < .001$

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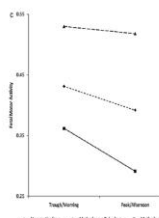


Fig. 3. Fetal data collected at Time 1 (through methadone) and Time 2 (peak methadone) in the two Methadone-exposed groups and at comparable morning and afternoon times in the Non-Methadone group. Neonates differ significantly in sleep (a). The Methadone + Poly-drug group showed significantly greater 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), and a trend level difference as compared to the Methadone only (MMO) 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 the properties of time engaged in motor activity during the 1-h recording, sleep did not differ over time.

RESEARCH

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OBSTETRICS

Methadone and perinatal outcomes: a retrospective cohort study

Brian J. Cleary, MD; Jean M. Donnelly, MB, BCh, BAQ; Judith D. Strawbridge, MS; Paul J. Gallagher, PhD; Tom Fahy, 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;204:138.e1–9.

RESEARCH

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Maternal and perinatal outcomes by methadone exposure							
Variable	n	Exposed n = 618 (1%)	Not exposed n = 59,412 (99%)	ORs 95% CI	Adjusted ORs (95% CI)		
Weeks of delivery	61,032						
Spontaneous vaginal	421 (68.0)	35 (5.6)	1	1	1		
Elective lower segment cesarean section	40 (6.5)	473 (75.8)	0.78	0.55–1.05	1.72	1.26–2.30	
Emergency lower segment cesarean section	71 (11.5)	746 (12.4)	0.85	0.66–1.09	1.26	0.94–1.68	
Emergency cesarean section	75 (12.1)	861 (13.9)	0.71	0.53–0.90	1.45	1.03–1.95	
Preterm delivery <37 wk	40,033	79 (17.4)	803 (1.3)	0.93	0.63–1.39	0.89	0.53–1.49
Preterm birth <37 wk	60,979	128 (20.4)	1,085 (1.8)	4.32	3.54–5.27	2.47	1.97–3.11
Spontaneous preterm	90 (14.5)	200 (32.4)	1.08	0.66–1.76	2.68	2.06–3.49	
Very preterm birth <32 wk	60,979	27 (4.4)	727 (1.2)	3.75	2.53–5.56	2.27	1.40–3.69
Preterm delivery <32 wk	72 (11.6)	363 (58.6)	0.71	0.34–1.47	2.89	1.69–5.29	
Small for gestational age <10th percentile	59,877	200 (32.4)	6279 (10.5)	0.70	0.57–0.87	2.21	1.60–2.94
Very small for gestational age <3rd percentile	60,725	29 (4.7)	638 (1.1)	3.18	2.02–5.00	1.94	1.12–3.37
Very small for gestational age <1st percentile	60,979	22 (3.6)	680 (1.1)	2.28	1.23–4.00	2.07	1.23–3.46
Neonatal admission to neonatal intensive care unit	60,977	61 (10)	369 (0.6)	1.68	0.86–3.32	0.87	0.33–2.31
Admission to neonatal unit	61,029	328 (53.1)	8778 (14.8)	6.69	5.70–7.85	6.15	5.14–7.36
Conjugate abnormal	61,029	47 (7.6)	1778 (2.9)	2.71	2.01–3.67	2.89	1.94–4.34
Meconium	22 (3.6)	442 (71.8)	2.81	1.70–4.62	2.12	1.26–3.56	
Meconium	194 (31.7)	647 (105)	3.87	3.14–4.80	1.90	1.10–3.40	
Chromosomal	1 (0.16)	100 (16.3)	0.65	0.04–10.46	1.48	0.19–11.4	
Unexplained	5 (0.81)	100 (16.3)	2.87	1.04–7.9	7.86	2.58–24.4	
Perinatal death	61,030	10 (1.6)	497 (0.8)	2.04	1.00–4.11	1.70	0.87–3.30
Neonatal abstinence syndrome	61,029	247 (40.0)	39 (0.6)	10.00	7.28–13.64	426	289–729

RESEARCH

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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 conotruncal cardiac 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 gastrochisis (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 Methadone ??

- ◉ 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 Paediatrica 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 Paediatrica 2008
Hudak et al; Pediatrics 2012

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

F392

Kuschel, Austerberry, Cornwell, et al

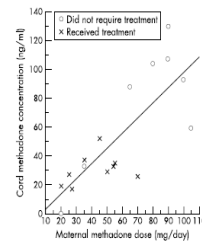


Figure 1 Relation between maternal methadone dose and cord methadone concentration. $R^2 = 0.59$, $p < 0.0001$.

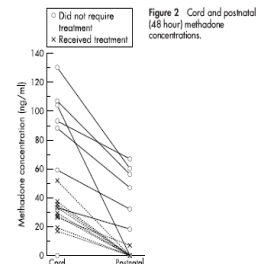


Figure 2 Cord and postnatal (48 hour) methadone concentrations.

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 Paediatrica* 2008

Alton 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!

Parent Name	1. Date (mm/dd/yyyy)	2. Time (mm/dd/yyyy)	3. Bed (mm/dd/yyyy)	4. Room (mm/dd/yyyy)	5. Score
<p>1. General Appearance</p> <p>2. States 1-3 in after feeding</p> <p>3. States 1-3 in after feeding</p> <p>4. States 1-3 in after feeding</p> <p>5. States 1-3 in after feeding</p> <p>6. States 1-3 in after feeding</p> <p>7. States 1-3 in after feeding</p> <p>8. States 1-3 in after feeding</p> <p>9. States 1-3 in after feeding</p> <p>10. States 1-3 in after feeding</p> <p>11. States 1-3 in after feeding</p> <p>12. States 1-3 in after feeding</p> <p>13. States 1-3 in after feeding</p> <p>14. States 1-3 in after feeding</p> <p>15. States 1-3 in after feeding</p> <p>16. States 1-3 in after feeding</p> <p>17. States 1-3 in after feeding</p> <p>18. States 1-3 in after feeding</p> <p>19. States 1-3 in after feeding</p> <p>20. States 1-3 in after feeding</p> <p>21. States 1-3 in after feeding</p> <p>22. States 1-3 in after feeding</p> <p>23. States 1-3 in after feeding</p> <p>24. States 1-3 in after feeding</p> <p>25. States 1-3 in after feeding</p> <p>26. States 1-3 in after feeding</p> <p>27. States 1-3 in after feeding</p> <p>28. States 1-3 in after feeding</p> <p>29. States 1-3 in after feeding</p> <p>30. States 1-3 in after feeding</p> <p>31. States 1-3 in after feeding</p> <p>32. States 1-3 in after feeding</p> <p>33. States 1-3 in after feeding</p> <p>34. States 1-3 in after feeding</p> <p>35. States 1-3 in after feeding</p> <p>36. States 1-3 in after feeding</p> <p>37. States 1-3 in after feeding</p> <p>38. States 1-3 in after feeding</p> <p>39. States 1-3 in after feeding</p> <p>40. States 1-3 in after feeding</p> <p>41. States 1-3 in after feeding</p> <p>42. States 1-3 in after feeding</p> <p>43. States 1-3 in after feeding</p> <p>44. States 1-3 in after feeding</p> <p>45. States 1-3 in after feeding</p> <p>46. States 1-3 in after feeding</p> <p>47. States 1-3 in after feeding</p> <p>48. States 1-3 in after feeding</p> <p>49. States 1-3 in after feeding</p> <p>50. States 1-3 in after feeding</p> <p>51. States 1-3 in after feeding</p> <p>52. States 1-3 in after feeding</p> <p>53. States 1-3 in after feeding</p> <p>54. States 1-3 in after feeding</p> <p>55. States 1-3 in after feeding</p> <p>56. States 1-3 in after feeding</p> <p>57. States 1-3 in after feeding</p> <p>58. States 1-3 in after feeding</p> <p>59. States 1-3 in after feeding</p> <p>60. States 1-3 in after feeding</p> <p>61. States 1-3 in after feeding</p> <p>62. States 1-3 in after feeding</p> <p>63. States 1-3 in after feeding</p> <p>64. States 1-3 in after feeding</p> <p>65. States 1-3 in after feeding</p> <p>66. States 1-3 in after feeding</p> <p>67. States 1-3 in after feeding</p> <p>68. States 1-3 in after feeding</p> <p>69. States 1-3 in after feeding</p> <p>70. States 1-3 in after feeding</p> <p>71. States 1-3 in after feeding</p> <p>72. States 1-3 in after feeding</p> <p>73. States 1-3 in after feeding</p> <p>74. States 1-3 in after feeding</p> <p>75. States 1-3 in after feeding</p> <p>76. States 1-3 in after feeding</p> <p>77. States 1-3 in after feeding</p> <p>78. States 1-3 in after feeding</p> <p>79. States 1-3 in after feeding</p> <p>80. States 1-3 in after feeding</p> <p>81. States 1-3 in after feeding</p> <p>82. States 1-3 in after feeding</p> <p>83. States 1-3 in after feeding</p> <p>84. States 1-3 in after feeding</p> <p>85. States 1-3 in after feeding</p> <p>86. States 1-3 in after feeding</p> <p>87. States 1-3 in after feeding</p> <p>88. States 1-3 in after feeding</p> <p>89. States 1-3 in after feeding</p> <p>90. States 1-3 in after feeding</p> <p>91. States 1-3 in after feeding</p> <p>92. States 1-3 in after feeding</p> <p>93. States 1-3 in after feeding</p> <p>94. States 1-3 in after feeding</p> <p>95. States 1-3 in after feeding</p> <p>96. States 1-3 in after feeding</p> <p>97. States 1-3 in after feeding</p> <p>98. States 1-3 in after feeding</p> <p>99. States 1-3 in after feeding</p> <p>100. States 1-3 in after feeding</p>					

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

TABLE 4. Neonatal Drug-Withdrawal Scoring System

Signs	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 Paediatrica* 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 Gabrielle 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

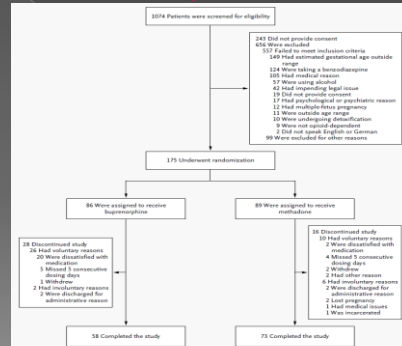


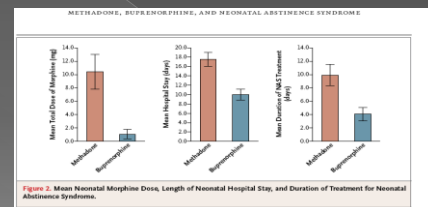
Figure 1. Screening, Randomization, and Rate of Treatment Completion, According to Study Group.

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	3.3±0.7		<0.0001†
Duration of infant's hospital stay — days	17.5±1.5	10.6±1.2		<0.0001†
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		<0.00122‡
Weight at birth — g	2878.5±66.3	3036.7±72.6		0.03
Length at birth — cm	47.8±0.5	49.8±0.5		0.005
Protrusion, <2 wk — no. (%)	14 (19)	4 (7)	0.3 (0.1–2.0)	0.37
Gestational age at delivery — wk	37.9±0.3	38.1±0.3		0.307
Apgar score				
1 min	8.0±0.2	8.1±0.2		0.87
5 min	9.0±0.1	9.0±0.1		0.89
Secondary maternal outcomes				
Cesarean section — no. (%)	27 (37)	17 (29)	0.6 (0.2–2.0)	0.33
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)	0.39
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. (%)	17 (23)	18 (31)	0.5 (0.2–0.9)	0.03
Did not complete study — no. (%)	16 (22)	28 (48)	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



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. Gaudena¹, Teresa Linares Scott¹, Sarah H. Heil^{1,2}, Mara G. Cople³, Karol Kaltenbach⁴, Gary J. Badger⁵, Amelia M. Arista⁶, Susan M. Stone⁷, Peter R. Martin⁸ & Hendrie E. Jones^{1,9}

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
Shoop	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
Hypertensive Moro reflex	55 (76)	33 (58)	0.03
Sneezing	55 (76)	51 (89)	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
Excitation	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

Values shown in bold type indicate significant differences between medication conditions. NAS = neonatal abstinence syndrome.

Addiction

RESEARCH REPORT

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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

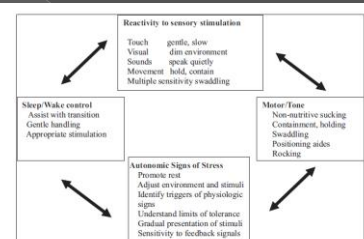


FIGURE 3. Nonpharmacologic care by domain for the infant affected by neonatal abstinence syndrome.

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

Janzon 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

<i>Opioid withdrawal</i>		<i>Polydrug withdrawal</i>	
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, 65%)	Phenobarbital (24) Intravenous morphine (10) Methadone (8) Clonidine (5) Diazepam (2) Oral morphine (6) Phenobarbital (4) Tincture of opium (5) Clonidine (2) Oral morphine (4) Methadone (4) Tincture of opium (5) Diazepam (2)	Opioids (39, 52%)	Phenobarbital (27) Methadone (5) Clonidine (2) Diazepam (1) Variable (6) Opioids (8) Diazepam (8) Methadone (4) Randy seen (4) Phenobarbital (4) Opioids (3) Diazepam (1)
Methadone (15, 20%)		Phenobarbital (24, 32%)	
Phenobarbital (13, 17.5%)		Methadone (8, 10.6%)	
		Randy 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 tailor online and anticipate treatment response based on the new data infrastructure.

Neonatal Abstinence Syndrome (NAS) Research:

- The groundbreaking research on NAS, commonly referred to as "drug addicted babies," is recent and timely due to the unfortunate, growing trend of opiate and other substance abuse. Preliminary research suggests that in 2011 alone, 650 babies were born with NAS and treated at 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 expanded 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 exposure 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; response 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 serving 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 USDITL card-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
 - Adapt 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!

Parent Name	DOB (mm/dd/yyyy)	Medical Record #	Room #	Unit	Ward	Room
<p>Modified Finnegan Scoring</p> <p>1. Sleepless cry 0-2 2. Exaggerated cry 0-2 3. Tremor 1 hr after feeding 0-2 4. Tremor 2 hrs after feeding 0-2 5. Tremor 3 hrs after feeding 0-2 6. Irritability when held 0-2 7. Hyperactive or irritable when held 0-2 8. Sustained head extension 0-2 9. Sustained head extension 0-2 10. Sustained head extension 0-2 11. Sustained head extension 0-2 12. Sustained head extension 0-2 13. Sustained head extension 0-2 14. Sustained head extension 0-2 15. Sustained head extension 0-2 16. Sustained head extension 0-2 17. Sustained head extension 0-2 18. Sustained head extension 0-2 19. Sustained head extension 0-2 20. Sustained head extension 0-2</p>						
<p>Scoring instructions:</p> <p>1. If infant scores 1-8, receive 1 mg morphine in 1 hour. 2. If infant scores 9-10, receive 2 mg morphine in 1 hour. 3. If infant scores 11-12, receive 3 mg morphine in 1 hour. 4. If infant scores 13-14, receive 4 mg morphine in 1 hour. 5. If infant scores 15-16, receive 5 mg morphine in 1 hour. 6. If infant scores 17-18, receive 6 mg morphine in 1 hour. 7. If infant scores 19-20, receive 7 mg morphine in 1 hour. 8. If infant scores 21-22, receive 8 mg morphine in 1 hour. 9. If infant scores 23-24, receive 9 mg morphine in 1 hour. 10. If infant scores 25-26, receive 10 mg morphine in 1 hour. 11. If infant scores 27-28, receive 11 mg morphine in 1 hour. 12. If infant scores 29-30, receive 12 mg morphine in 1 hour. 13. If infant scores 31-32, receive 13 mg morphine in 1 hour. 14. If infant scores 33-34, receive 14 mg morphine in 1 hour. 15. If infant scores 35-36, receive 15 mg morphine in 1 hour. 16. If infant scores 37-38, receive 16 mg morphine in 1 hour. 17. If infant scores 39-40, receive 17 mg morphine in 1 hour. 18. If infant scores 41-42, receive 18 mg morphine in 1 hour. 19. If infant scores 43-44, receive 19 mg morphine in 1 hour. 20. If infant scores 45-46, receive 20 mg morphine in 1 hour. 21. If infant scores 47-48, receive 21 mg morphine in 1 hour. 22. If infant scores 49-50, receive 22 mg morphine in 1 hour. 23. If infant scores 51-52, receive 23 mg morphine in 1 hour. 24. If infant scores 53-54, receive 24 mg morphine in 1 hour. 25. If infant scores 55-56, receive 25 mg morphine in 1 hour. 26. If infant scores 57-58, receive 26 mg morphine in 1 hour. 27. If infant scores 59-60, receive 27 mg morphine in 1 hour. 28. If infant scores 61-62, receive 28 mg morphine in 1 hour. 29. If infant scores 63-64, receive 29 mg morphine in 1 hour. 30. If infant scores 65-66, receive 30 mg morphine in 1 hour. 31. If infant scores 67-68, receive 31 mg morphine in 1 hour. 32. If infant scores 69-70, receive 32 mg morphine in 1 hour. 33. If infant scores 71-72, receive 33 mg morphine in 1 hour. 34. If infant scores 73-74, receive 34 mg morphine in 1 hour. 35. If infant scores 75-76, receive 35 mg morphine in 1 hour. 36. If infant scores 77-78, receive 36 mg morphine in 1 hour. 37. If infant scores 79-80, receive 37 mg morphine in 1 hour. 38. If infant scores 81-82, receive 38 mg morphine in 1 hour. 39. If infant scores 83-84, receive 39 mg morphine in 1 hour. 40. If infant scores 85-86, receive 40 mg morphine in 1 hour. 41. If infant scores 87-88, receive 41 mg morphine in 1 hour. 42. If infant scores 89-90, receive 42 mg morphine in 1 hour. 43. If infant scores 91-92, receive 43 mg morphine in 1 hour. 44. If infant scores 93-94, receive 44 mg morphine in 1 hour. 45. If infant scores 95-96, receive 45 mg morphine in 1 hour. 46. If infant scores 97-98, receive 46 mg morphine in 1 hour. 47. If infant scores 99-100, receive 47 mg morphine in 1 hour. 48. If infant scores 101-102, receive 48 mg morphine in 1 hour. 49. If infant scores 103-104, receive 49 mg morphine in 1 hour. 50. If infant scores 105-106, receive 50 mg morphine in 1 hour. 51. If infant scores 107-108, receive 51 mg morphine in 1 hour. 52. If infant scores 109-110, receive 52 mg morphine in 1 hour. 53. If infant scores 111-112, receive 53 mg morphine in 1 hour. 54. If infant scores 113-114, receive 54 mg morphine in 1 hour. 55. If infant scores 115-116, receive 55 mg morphine in 1 hour. 56. If infant scores 117-118, receive 56 mg morphine in 1 hour. 57. If infant scores 119-120, receive 57 mg morphine in 1 hour. 58. If infant scores 121-122, receive 58 mg morphine in 1 hour. 59. If infant scores 123-124, receive 59 mg morphine in 1 hour. 60. If infant scores 125-126, receive 60 mg morphine in 1 hour. 61. If infant scores 127-128, receive 61 mg morphine in 1 hour. 62. If infant scores 129-130, receive 62 mg morphine in 1 hour. 63. If infant scores 131-132, receive 63 mg morphine in 1 hour. 64. If infant scores 133-134, receive 64 mg morphine in 1 hour. 65. If infant scores 135-136, receive 65 mg morphine in 1 hour. 66. If infant scores 137-138, receive 66 mg morphine in 1 hour. 67. If infant scores 139-140, receive 67 mg morphine in 1 hour. 68. If infant scores 141-142, receive 68 mg morphine in 1 hour. 69. If infant scores 143-144, receive 69 mg morphine in 1 hour. 70. If infant scores 145-146, receive 70 mg morphine in 1 hour. 71. If infant scores 147-148, receive 71 mg morphine in 1 hour. 72. If infant scores 149-150, receive 72 mg morphine in 1 hour. 73. If infant scores 151-152, receive 73 mg morphine in 1 hour. 74. If infant scores 153-154, receive 74 mg morphine in 1 hour. 75. If infant scores 155-156, receive 75 mg morphine in 1 hour. 76. If infant scores 157-158, receive 76 mg morphine in 1 hour. 77. If infant scores 159-160, receive 77 mg morphine in 1 hour. 78. If infant scores 161-162, receive 78 mg morphine in 1 hour. 79. If infant scores 163-164, receive 79 mg morphine in 1 hour. 80. If infant scores 165-166, receive 80 mg morphine in 1 hour. 81. If infant scores 167-168, receive 81 mg morphine in 1 hour. 82. If infant scores 169-170, receive 82 mg morphine in 1 hour. 83. If infant scores 171-172, receive 83 mg morphine in 1 hour. 84. If infant scores 173-174, receive 84 mg morphine in 1 hour. 85. If infant scores 175-176, receive 85 mg morphine in 1 hour. 86. If infant scores 177-178, receive 86 mg morphine in 1 hour. 87. If infant scores 179-180, receive 87 mg morphine in 1 hour. 88. If infant scores 181-182, receive 88 mg morphine in 1 hour. 89. If infant scores 183-184, receive 89 mg morphine in 1 hour. 90. If infant scores 185-186, receive 90 mg morphine in 1 hour. 91. If infant scores 187-188, receive 91 mg morphine in 1 hour. 92. If infant scores 189-190, receive 92 mg morphine in 1 hour. 93. If infant scores 191-192, receive 93 mg morphine in 1 hour. 94. If infant scores 193-194, receive 94 mg morphine in 1 hour. 95. If infant scores 195-196, receive 95 mg morphine in 1 hour. 96. If infant scores 197-198, receive 96 mg morphine in 1 hour. 97. If infant scores 199-200, receive 97 mg morphine in 1 hour. 98. If infant scores 201-202, receive 98 mg morphine in 1 hour. 99. If infant scores 203-204, receive 99 mg morphine in 1 hour. 100. If infant scores 205-206, receive 100 mg morphine in 1 hour. 101. If infant scores 207-208, receive 101 mg morphine in 1 hour. 102. If infant scores 209-210, receive 102 mg morphine in 1 hour. 103. If infant scores 211-212, receive 103 mg morphine in 1 hour. 104. If infant scores 213-214, receive 104 mg morphine in 1 hour. 105. If infant scores 215-216, receive 105 mg morphine in 1 hour. 106. If infant scores 217-218, receive 106 mg morphine in 1 hour. 107. If infant scores 219-220, receive 107 mg morphine in 1 hour. 108. If infant scores 221-222, receive 108 mg morphine in 1 hour. 109. If infant scores 223-224, receive 109 mg morphine in 1 hour. 110. If infant scores 225-226, receive 110 mg morphine in 1 hour. 111. If infant scores 227-228, receive 111 mg morphine in 1 hour. 112. If infant scores 229-230, receive 112 mg morphine in 1 hour. 113. If infant scores 231-232, receive 113 mg morphine in 1 hour. 114. If infant scores 233-234, receive 114 mg morphine in 1 hour. 115. If infant scores 235-236, receive 115 mg morphine in 1 hour. 116. If infant scores 237-238, receive 116 mg morphine in 1 hour. 117. If infant scores 239-240, receive 117 mg morphine in 1 hour. 118. If infant scores 241-242, receive 118 mg morphine in 1 hour. 119. If infant scores 243-244, receive 119 mg morphine in 1 hour. 120. If infant scores 245-246, receive 120 mg morphine in 1 hour. 121. If infant scores 247-248, receive 121 mg morphine in 1 hour. 122. If infant scores 249-250, receive 122 mg morphine in 1 hour. 123. If infant scores 251-252, receive 123 mg morphine in 1 hour. 124. If infant scores 253-254, receive 124 mg morphine in 1 hour. 125. If infant scores 255-256, receive 125 mg morphine in 1 hour. 126. If infant scores 257-258, receive 126 mg morphine in 1 hour. 127. If infant scores 259-260, receive 127 mg morphine in 1 hour. 128. If infant scores 261-262, receive 128 mg morphine in 1 hour. 129. If infant scores 263-264, receive 129 mg morphine in 1 hour. 130. If infant scores 265-266, receive 130 mg morphine in 1 hour. 131. If infant scores 267-268, receive 131 mg morphine in 1 hour. 132. If infant scores 269-270, receive 132 mg morphine in 1 hour. 133. If infant scores 271-272, receive 133 mg morphine in 1 hour. 134. If infant scores 273-274, receive 134 mg morphine in 1 hour. 135. If infant scores 275-276, receive 135 mg morphine in 1 hour. 136. If infant scores 277-278, receive 136 mg morphine in 1 hour. 137. If infant scores 279-280, receive 137 mg morphine in 1 hour. 138. If infant scores 281-282, receive 138 mg morphine in 1 hour. 139. If infant scores 283-284, receive 139 mg morphine in 1 hour. 140. If infant scores 285-286, receive 140 mg morphine in 1 hour. 141. If infant scores 287-288, receive 141 mg morphine in 1 hour. 142. If infant scores 289-290, receive 142 mg morphine in 1 hour. 143. If infant scores 291-292, receive 143 mg morphine in 1 hour. 144. If infant scores 293-294, receive 144 mg morphine in 1 hour. 145. If infant scores 295-296, receive 145 mg morphine in 1 hour. 146. If infant scores 297-298, receive 146 mg morphine in 1 hour. 147. If infant scores 299-300, receive 147 mg morphine in 1 hour. 148. If infant scores 301-302, receive 148 mg morphine in 1 hour. 149. If infant scores 303-304, receive 149 mg morphine in 1 hour. 150. If infant scores 305-306, receive 150 mg morphine in 1 hour. 151. If infant scores 307-308, receive 151 mg morphine in 1 hour. 152. If infant scores 309-310, receive 152 mg morphine in 1 hour. 153. If infant scores 311-312, receive 153 mg morphine in 1 hour. 154. If infant scores 313-314, receive 154 mg morphine in 1 hour. 155. If infant scores 315-316, receive 155 mg morphine in 1 hour. 156. If infant scores 317-318, receive 156 mg morphine in 1 hour. 157. If infant scores 319-320, receive 157 mg morphine in 1 hour. 158. If infant scores 321-322, receive 158 mg morphine in 1 hour. 159. If infant scores 323-324, receive 159 mg morphine in 1 hour. 160. If infant scores 325-326, receive 160 mg morphine in 1 hour. 161. If infant scores 327-328, receive 161 mg morphine in 1 hour. 162. If infant scores 329-330, receive 162 mg morphine in 1 hour. 163. If infant scores 331-332, receive 163 mg morphine in 1 hour. 164. If infant scores 333-334, receive 164 mg morphine in 1 hour. 165. If infant scores 335-336, receive 165 mg morphine in 1 hour. 166. If infant scores 337-338, receive 166 mg morphine in 1 hour. 167. If infant scores 339-340, receive 167 mg morphine in 1 hour. 168. If infant scores 341-342, receive 168 mg morphine in 1 hour. 169. If infant scores 343-344, receive 169 mg morphine in 1 hour. 170. If infant scores 345-346, receive 170 mg morphine in 1 hour. 171. If infant scores 347-348, receive 171 mg morphine in 1 hour. 172. If infant scores 349-350, receive 172 mg morphine in 1 hour. 173. If infant scores 351-352, receive 173 mg morphine in 1 hour. 174. If infant scores 353-354, receive 174 mg morphine in 1 hour. 175. If infant scores 355-356, receive 175 mg morphine in 1 hour. 176. If infant scores 357-358, receive 176 mg morphine in 1 hour. 177. If infant scores 359-360, receive 177 mg morphine in 1 hour. 178. If infant scores 361-362, receive 178 mg morphine in 1 hour. 179. If infant scores 363-364, receive 179 mg morphine in 1 hour. 180. If infant scores 365-366, receive 180 mg morphine in 1 hour. 181. If infant scores 367-368, receive 181 mg morphine in 1 hour. 182. If infant scores 369-370, receive 182 mg morphine in 1 hour. 183. If infant scores 371-372, receive 183 mg morphine in 1 hour. 184. If infant scores 373-374, receive 184 mg morphine in 1 hour. 185. If infant scores 375-376, receive 185 mg morphine in 1 hour. 186. If infant scores 377-378, receive 186 mg morphine in 1 hour. 187. If infant scores 379-380, receive 187 mg morphine in 1 hour. 188. If infant scores 381-382, receive 188 mg morphine in 1 hour. 189. If infant scores 383-384, receive 189 mg morphine in 1 hour. 190. If infant scores 385-386, receive 190 mg morphine in 1 hour. 191. If infant scores 387-388, receive 191 mg morphine in 1 hour. 192. If infant scores 389-390, receive 192 mg morphine in 1 hour. 193. If infant scores 391-392, receive 193 mg morphine in 1 hour. 194. If infant scores 393-394, receive 194 mg morphine in 1 hour. 195. If infant scores 395-396, receive 195 mg morphine in 1 hour. 196. If infant scores 397-398, receive 196 mg morphine in 1 hour. 197. If infant scores 399-400, receive 197 mg morphine in 1 hour. 198. If infant scores 401-402, receive 198 mg morphine in 1 hour. 199. If infant scores 403-404, receive 199 mg morphine in 1 hour. 200. If infant scores 405-406, receive 200 mg morphine in 1 hour. 201. If infant scores 407-408, receive 201 mg morphine in 1 hour. 202. If infant scores 409-410, receive 202 mg morphine in 1 hour. 203. If infant scores 411-412, receive 203 mg morphine in 1 hour. 204. If infant scores 413-414, receive 204 mg morphine in 1 hour. 205. If infant scores 415-416, receive 205 mg morphine in 1 hour. 206. If infant scores 417-418, receive 206 mg morphine in 1 hour. 207. If infant scores 419-420, receive 207 mg morphine in 1 hour. 208. If infant scores 421-422, receive 208 mg morphine in 1 hour. 209. If infant scores 423-424, receive 209 mg morphine in 1 hour. 210. If infant scores 425-426, receive 210 mg morphine in 1 hour. 211. If infant scores 427-428, receive 211 mg morphine in 1 hour. 212. If infant scores 429-430, receive 212 mg morphine in 1 hour. 213. If infant scores 431-432, receive 213 mg morphine in 1 hour. 214. If infant scores 433-434, receive 214 mg morphine in 1 hour. 215. If infant scores 435-436, receive 215 mg morphine in 1 hour. 216. If infant scores 437-438, receive 216 mg morphine in 1 hour. 217. If infant scores 439-440, receive 217 mg morphine in 1 hour. 218. If infant scores 441-442, receive 218 mg morphine in 1 hour. 219. If infant scores 443-444, receive 219 mg morphine in 1 hour. 220. If infant scores 445-446, receive 220 mg morphine in 1 hour. 221. If infant scores 447-448, receive 221 mg morphine in 1 hour. 222. If infant scores 449-450, receive 222 mg morphine in 1 hour. 223. If infant scores 451-452, receive 223 mg morphine in 1 hour. 224. If infant scores 453-454, receive 224 mg morphine in 1 hour. 225. If infant scores 455-456, receive 225 mg morphine in 1 hour. 226. If infant scores 457-458, receive 226 mg morphine in 1 hour. 227. If infant scores 459-460, receive 227 mg morphine in 1 hour. 228. If infant scores 461-462, receive 228 mg morphine in 1 hour. 229. If infant scores 463-464, receive 229 mg morphine in 1 hour. 230. If infant scores 465-466, receive 230 mg morphine in 1 hour. 231. If infant scores 467-468, receive 231 mg morphine in 1 hour. 232. If infant scores 469-470, receive 232 mg morphine in 1 hour. 233. If infant scores 471-472, receive 233 mg morphine in 1 hour. 234. If infant scores 473-474, receive 234 mg morphine in 1 hour. 235. If infant scores 475-476, receive 235 mg morphine in 1 hour. 236. If infant scores 477-478, receive 236 mg morphine in 1 hour. 237. If infant scores 479-480, receive 237 mg morphine in 1 hour. 238. If infant scores 481-482, receive 238 mg morphine in 1 hour. 239. If infant scores 483-484, receive 239 mg morphine in 1 hour. 240. If infant scores 485-486, receive 240 mg morphine in 1 hour. 241. If infant scores 487-488, receive 241 mg morphine in 1 hour. 242. If infant scores 489-490, receive 242 mg morphine in 1 hour. 243. If infant scores 491-492, receive 243 mg morphine in 1 hour. 244. If infant scores 493-494, receive 244 mg morphine in 1 hour. 245. If infant scores 495-496, receive 245 mg morphine in 1 hour. 246. If infant scores 497-498, receive 246 mg morphine in 1 hour. 247. If infant scores 499-500, receive 247 mg morphine in 1 hour. 248. If infant scores 501-502, receive 248 mg morphine in 1 hour. 249. If infant scores 503-504, receive 249 mg morphine in 1 hour. 250. If infant scores 505-506, receive 250 mg morphine in 1 hour. 251. If infant scores 507-508, receive 251 mg morphine in 1 hour. 252. If infant scores 509-510, receive 252 mg morphine in 1 hour. 253. If infant scores 511-512, receive 253 mg morphine in 1 hour. 254. If infant scores 513-514, receive 254 mg morphine in 1 hour. 255. If infant scores 515-516, receive 255 mg morphine in 1 hour. 256. If infant scores 517-518, receive 256 mg morphine in 1 hour. 257. If infant scores 519-520, receive 257 mg morphine in 1 hour. 258. If infant scores 521-522, receive 258 mg morphine in 1 hour. 259. If infant scores 523-524, receive 259 mg morphine in 1 hour. 260. If infant scores 525-526, receive 260 mg morphine in 1 hour. 261. If infant scores 527-528, receive 261 mg morphine in 1 hour. 262. If infant scores 529-530, receive 262 mg morphine in 1 hour. 263. If infant scores 531-532, receive 263 mg morphine in 1 hour. 264. If infant scores 533-534, receive 264 mg morphine in 1 hour. 265. If infant scores 535-536, receive 265 mg morphine in 1 hour. 266. If infant scores 537-538, receive 266 mg morphine in 1 hour. 267. If infant scores 539-540, receive 267 mg morphine in 1 hour. 268. If infant scores 541-542, receive 268 mg morphine in 1 hour. 269. If infant scores 543-544, receive 269 mg morphine in 1 hour. 270. If infant scores 545-546, receive 270 mg morphine in 1 hour. 271. If infant scores 547-548, receive 271 mg morphine in 1 hour. 272. If infant scores 549-550, receive 272 mg morphine in 1 hour. 273. If infant scores 551-552, receive 273 mg morphine in 1 hour. 274. If infant scores 553-554, receive 274 mg morphine in 1 hour. 275. If infant scores 555-556, receive 275 mg morphine in 1 hour. 276. If infant scores 557-558, receive 276 mg morphine in 1 hour. 277. If infant scores 559-560, receive 277 mg morphine in 1 hour. 278. If infant scores 561-562, receive 278 mg morphine in 1 hour. 279. If infant scores 563-564, receive 279 mg morphine in 1 hour. 280. If infant scores 565-566, receive 280 mg morphine in 1 hour. 281. If infant scores 567-568, receive 281 mg morphine in 1 hour. 282. If infant scores 569-570, receive 282 mg morphine in 1 hour. 283. If infant scores 571-572, receive 283 mg morphine in 1 hour. 284. If infant scores 573-574, receive 284 mg morphine in 1 hour. 285. If infant scores 575-576, receive 285 mg morphine in 1 hour. 286. If infant scores 577-578, receive 286 mg morphine in 1 hour. 287. If infant scores 579-580, receive 287 mg morphine in 1 hour. 288. If infant scores 581-582, receive 288 mg morphine in 1 hour. 289. If infant scores 583-584, receive 289 mg morphine in 1 hour. 290. If infant scores 585-586, receive 290 mg morphine in 1 hour. 291. If infant scores 587-588, receive 291 mg morphine in 1 hour. 292. If infant scores 589-590, receive 292 mg morphine in 1 hour. 293. If infant scores 591-592, receive 293 mg morphine in 1 hour. 294. If infant scores 593-594, receive 294 mg morphine in 1 hour. 295. If infant scores 595-596, receive 295 mg morphine in 1 hour. 296. If infant scores 597-598, receive 296 mg morphine in 1 hour. 297. If infant scores 599-600, receive 297 mg morphine in 1 hour. 298. If infant scores 601-602, receive 298 mg morphine in 1 hour. 299. If infant scores 603-604, receive 299 mg morphine in 1 hour. 300. If infant scores 605-606, receive 300 mg morphine in 1 hour. 301. If infant scores 607-608, receive 301 mg morphine in 1 hour. 302. If infant scores 609-610, receive 302 mg morphine in 1 hour. 303. If infant scores 611-612, receive 303 mg morphine in 1 hour. 304. If infant scores 613-614, receive 304 mg morphine in 1 hour. 305. If infant scores 615-616, receive 305 mg morphine in 1 hour. 306. If infant scores 617-618, receive 306 mg morphine in 1 hour. 307. If infant scores 619-620, receive 307 mg morphine in 1 hour. 308. If infant scores 621-622, receive 308 mg morphine in 1 hour. 309. If infant scores 623-624, receive 309 mg morphine in 1 hour. 310. If infant scores 625-626, receive 310 mg morphine in 1 hour. 311. If infant scores 627-628, receive 311 mg morphine in 1 hour. 312. If infant scores 629-630, receive 312 mg morphine in 1 hour. 313. If infant scores 631-632, receive 313 mg morphine in 1 hour. 314. If infant scores 633-634, receive 314 mg morphine in 1 hour. 315. If infant scores 635</p>						

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 the the two scores 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 sleep; infants should be monitored 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 0.02 mg every scoring period.
 - ii. For two scores in category II increase oral morphine by 0.04 mg every scoring period.
 - iii. For two scores in category III increase oral morphine by 0.06 mg every scoring period.
 - iv. For two scores in category IV increase oral morphine by 0.08 mg every scoring period.
 - v. For two scores in category V increase oral morphine by 0.10 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 \rightarrow 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 3/1/13

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