

Adverse Childhood Events and Neonatal Abstinence Syndrome Connecting the Dots

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- Nothing to Disclose
- No Conflicts of Interest

- Define the clinical presentation of Neonatal Drug Withdrawal/Neonatal Abstinence Syndrome
- Review the incidence of illicit drug abuse during pregnancy and the drugs most commonly abused
- Discuss the local and national incidence of Neonatal Abstinence Syndrome
- Discuss the methods of detection of illicit drug use during pregnancy
- Evaluate drugs used to treat Neonatal Abstinence Syndrome
- Discuss what we know about short & long term outcomes for affected infants
- Discuss the impact of other drugs on the fetus

Neonatal Abstinence Syndrome (NAS):

- A withdrawal syndrome that occurs in newborns after birth.
- The classic presentation is associated with opioid use during pregnancy.
- Not addiction
 - APA defines addiction as a chronic brain disease that causes compulsive substance use despite harmful consequences

Clinical Presentation is variable and dependent upon:

- Drug(s) misused
- The timing and the dose of the last drug used
 - The longer the $1/2$ life of the drug the later withdrawal symptoms will be seen
- Maternal and infant metabolism and excretion

Classic Symptoms of NAS

Central Nervous System Irritability

Autonomic System Dysfunction

Gastrointestinal Dysfunction

CNS Irritability

- Hypertonia
- Tremors
- Hyperreflexia
- Agitation and Restlessness
- High-pitched cry
- Sleep Disturbances
- Seizures – 2-11% of withdrawing infants



Autonomic System Dysfunction

- Yawning
- Nasal Stuffiness
- Sweating
- Sneezing
- Low-grade Fever
- Skin Mottling



Gastrointestinal Abnormalities

- Diarrhea
- Vomiting
- Poor Feeding
- Regurgitation
- Uncoordinated Swallow
- Failure to Thrive



Additional Symptoms

- Tachypnea
- Apnea
- Skin Excoriation



Symptoms may be present at birth, but often do not reach a peak until 2-3 days after delivery and may be delayed until 5-7 days of life.

AAP Recommendations:

Reasonable for neonates with known antenatal exposure to opiates and benzodiazepines to be “prudently observed” in the hospital for 4-7 days for signs of withdrawal.

Clinical Case - Nicholas

(Thanks to Gateway Health Plan, Mike Madden, M.D. and Robert Chico, M.D.)



Heroin



Methadone



Subutex

Demerol



Oxycontin



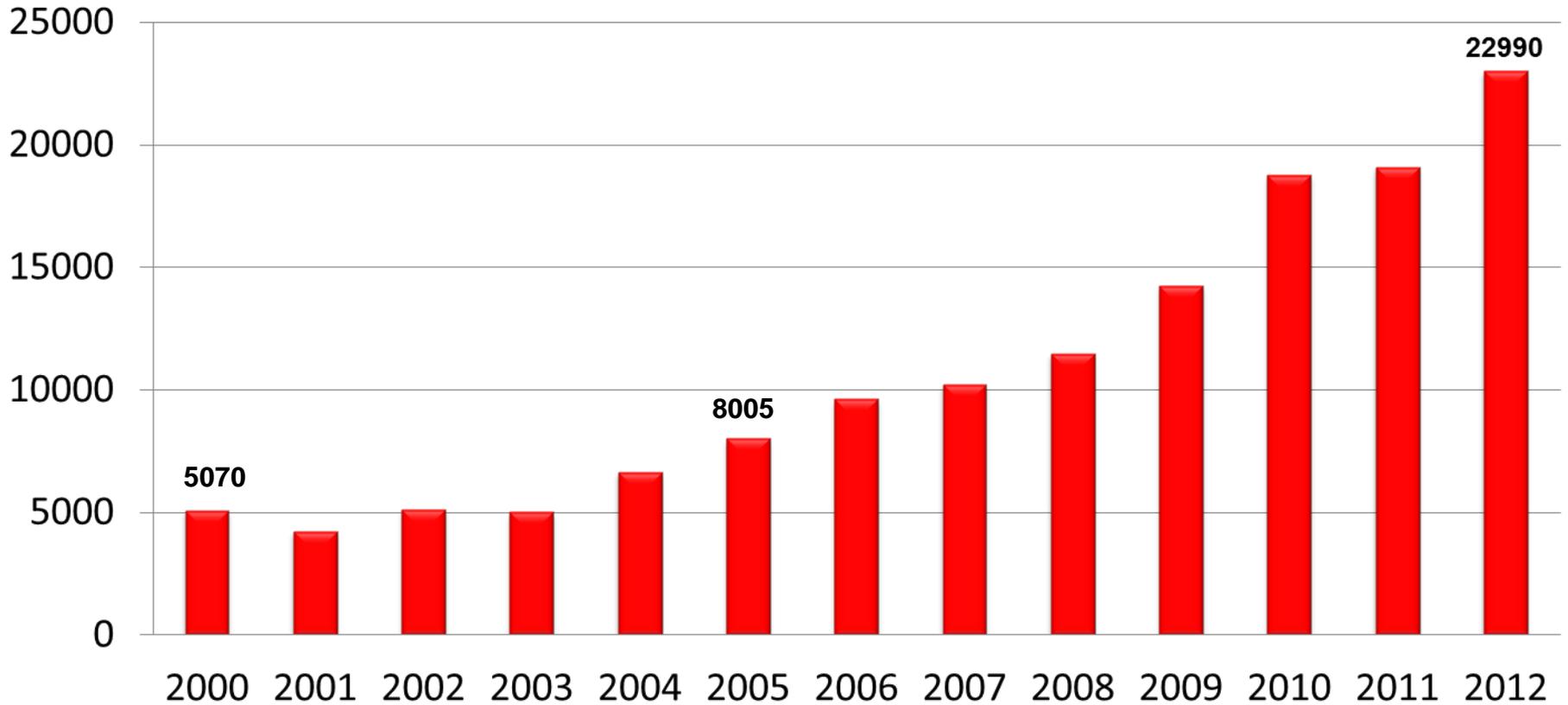
ZoHydro - ER

2013 National Survey on Drug Use & Health

- 5.4% of pregnant women between 15 to 44 years of age had used illicit drugs during the past month
 - Illicit drugs included marijuana/hashish, cocaine (including crack), inhalants, hallucinogens, heroin and prescription-type drugs used non-medically
 - 14.6% - 15-17 years of age
 - 8.6% - 18-25 years of age
 - 3.2% - 26-44 years of age

Data averaged from 2012-2013

National Incidence of NAS



Census Regions and Divisions of the United States



NORTHEAST

New England - 13.7%

Middle Atlantic - 6.8%

MIDWEST

East North Central – 6.9%

West North Central - 3.4%

SOUTH

South Atlantic - 6.9%

East South Central - 16.2%

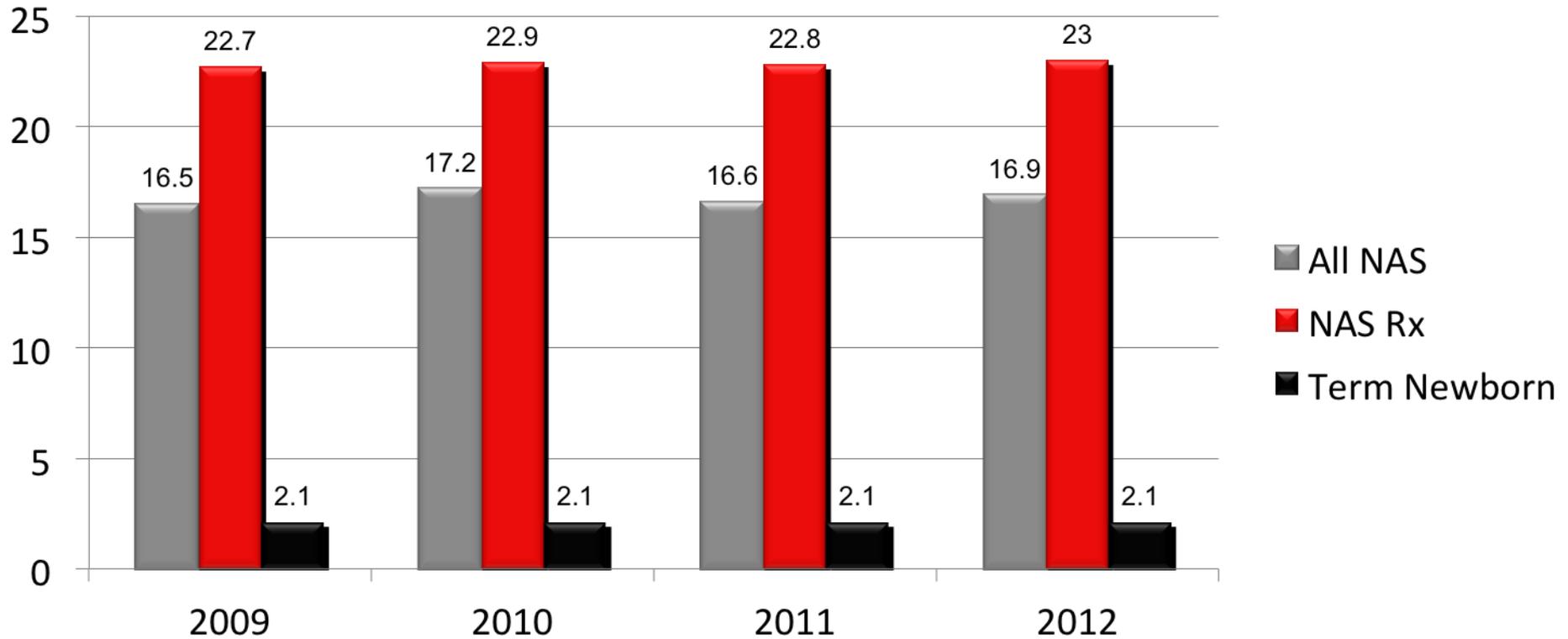
West South Central - 2.6%

WEST

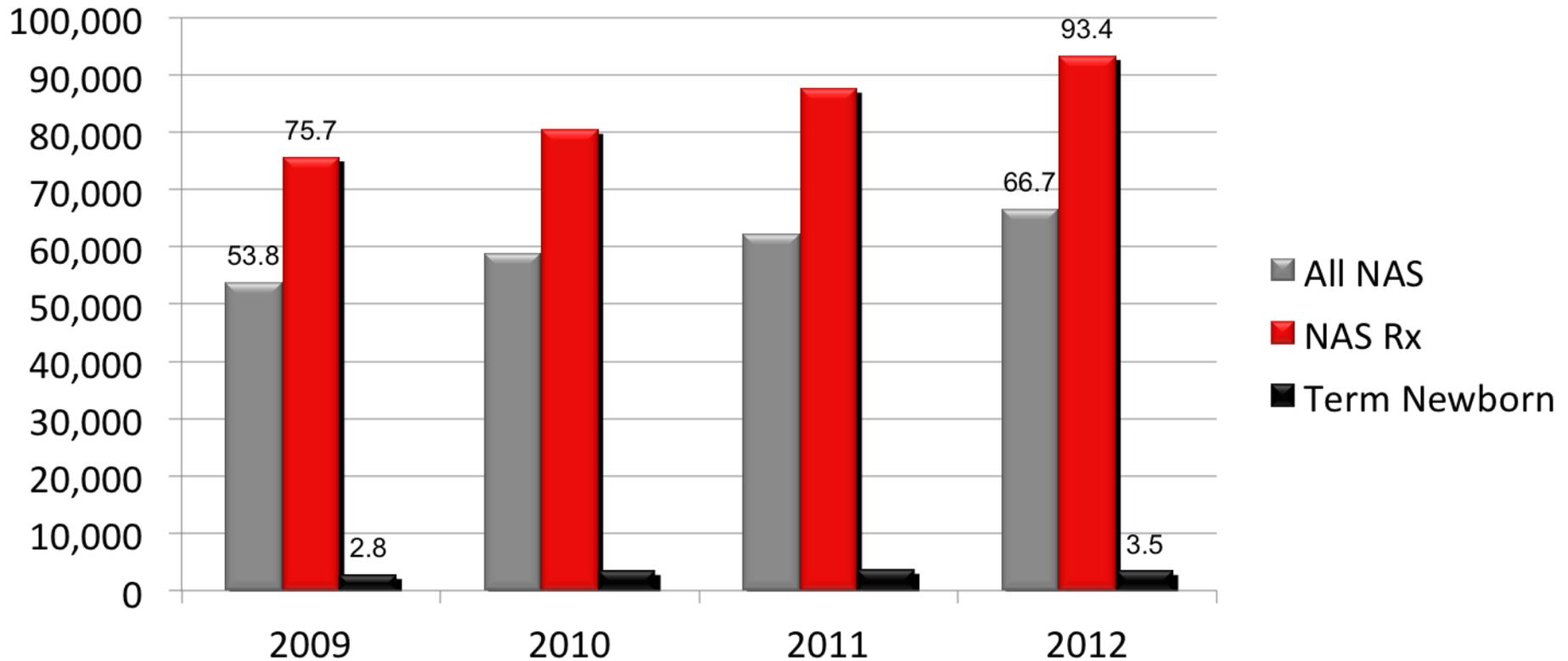
Mountain - 5.1%

Pacific - 3%

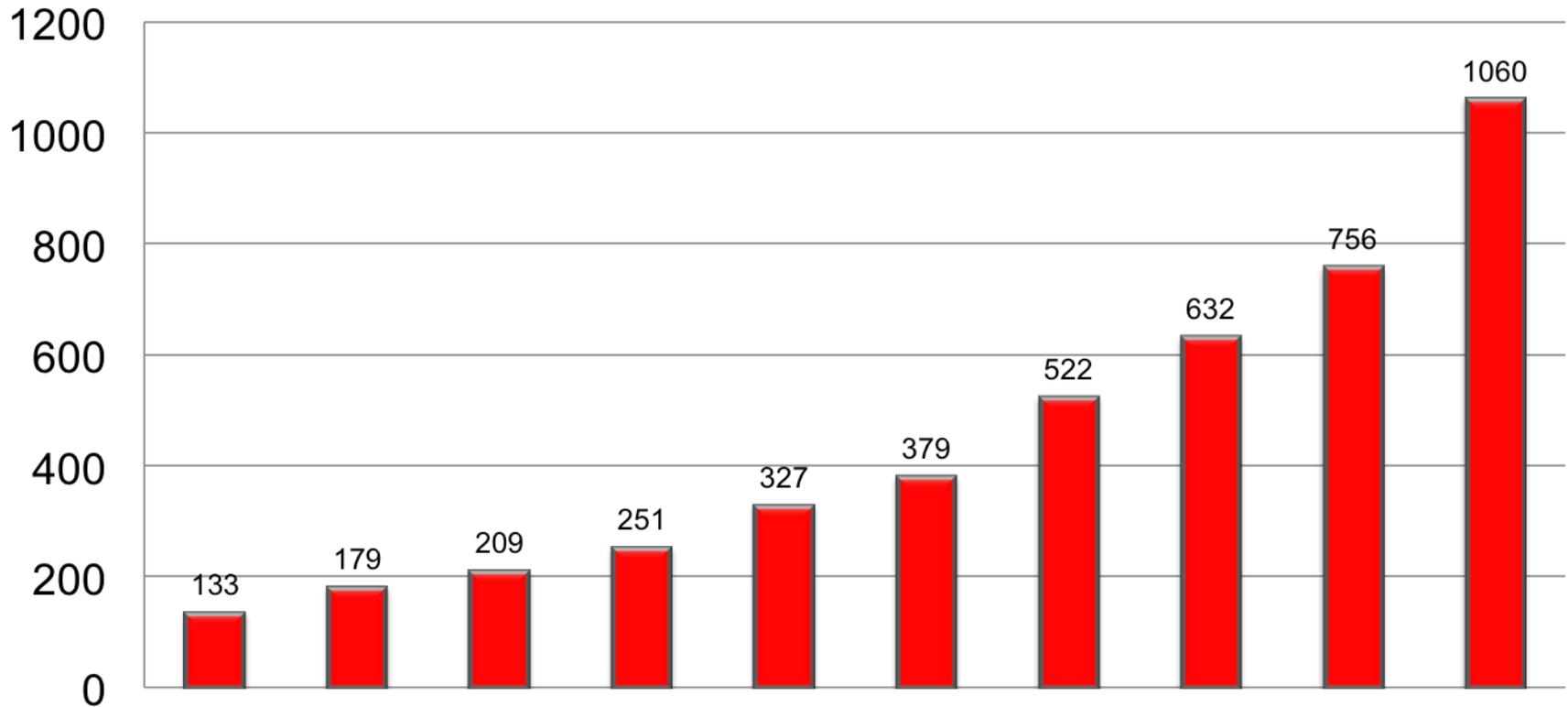
Mean Length of Hospital Stay



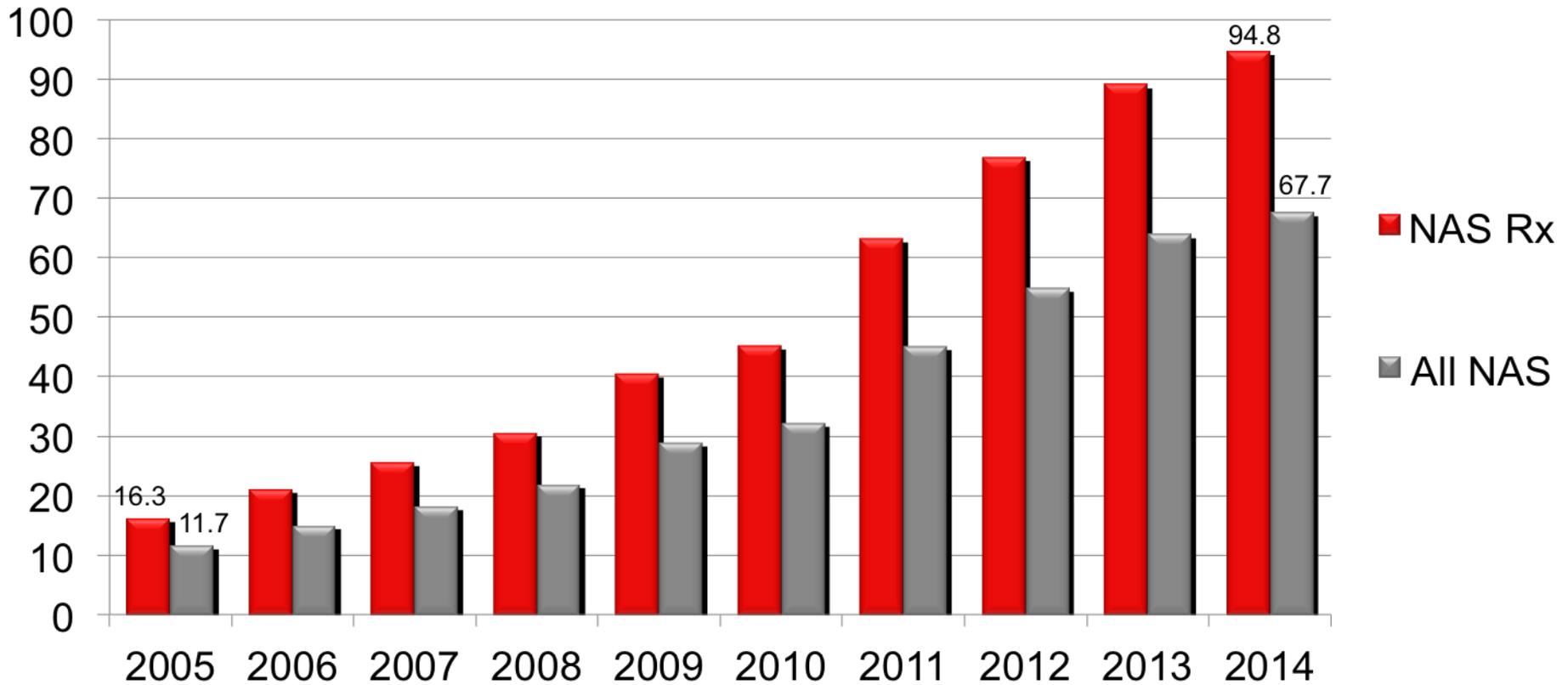
Inflation Adjusted Hospital Charges in Thousands 2012 US \$



NAS Hospitalizations of Kentucky Newborns



KY Cumulative Hospital Charges in Millions 2012 US \$



Addressing Opiate Abuse During Pregnancy

Screening

Current Maternal Indications for Screening

- No Prenatal Care
- Previous Unexplained Fetal Demise
- Precipitous Delivery
- Placental Abruption
- Repeated Spontaneous Abortions
- Cerebrovascular Accidents and Myocardial Infarctions

Current Neonatal Indications for Screening

- Maternal history of drug abuse
- Intrauterine growth restriction/small for gestational age
- Cardiovascular accidents in an otherwise healthy term infant
 - Myocardial Infarction, Stroke and Necrotizing Enterocolitis
- Signs and symptoms of drug withdrawal

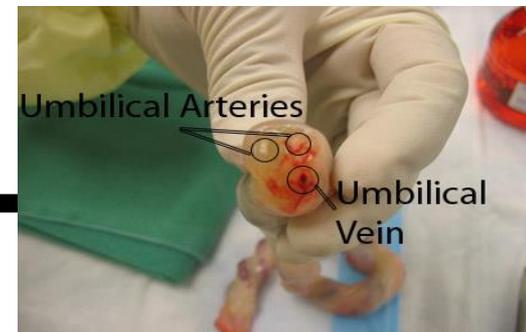


Screening in the Mother

Detailed Maternal Drug History

- Should be obtained if concern for drug use during pregnancy
 - Prescription and nonprescription drug intake
 - Herbal preparations used during pregnancy
 - The social habits of the parents
- Inexpensive and practical method for identifying substances of abuse
- Accurately determine timing of exposure
- Maternal self-reporting underestimates drug exposure

Identification of perinatal exposure is more likely if a biological specimen is collected in conjunction with a thorough history



No random biologic specimen identifies prenatal drug use with 100% accuracy

- A negative drug screening result does not ensure that the pregnancy was drug free
- Confirmation of the presence of a drug is not always associated with drug abuse

The use of any biological specimen
to determine timing and quantity
of prenatal exposure to
drugs of abuse is controversial

Maternal Urine

- Most drugs and their metabolites are found in higher concentrations in the urine of the mother than in her blood
 - Urine drug levels 100x that found in the plasma
 - It takes 6–8 hours or more post-consumption for drug to be metabolized and excreted in urine
- Opiates and benzodiazepines administered during labor and delivery may lead to positive urine toxicology screen

Urine screening may fail to identify drugs of abuse due to a limited time span for detection

- Alcohol 7-12 hours
- Marijuana
 - Single use 3 days
 - Moderate use 5-7 days
 - Daily use 10-15 days
 - Long term use >30 days
- Cocaine 2-4 days
- PCP 2-4 days
- Opioids
 - Heroin 2 days
 - Morphine 2-3 days
 - Oxycodone 2-4 days
 - Methadone 3 days
- Methamphetamines 2 days
- Benzodiazepines
 - Short acting 3 days
 - Long acting 30 days



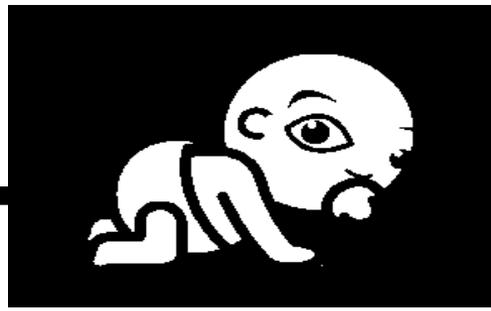
Screening in the Neonate

Neonatal Urine

- Advantages
 - Noninvasive matrix
- Disadvantages
 - Limited urinary output in the immediate postnatal period
 - Only identifies recent drug use
 - Difficult to obtain first voided specimen
 - The neonatal kidneys have a delayed ability to concentrate urine
 - The concentration of substances of abuse in the urine often falls below the federally established thresholds for detection

Meconium

- Advantages
 - Noninvasive matrix unique to the neonate
 - Identifies substances abused by the mother from the beginning of the second trimester until birth.
 - 93% sensitivity
- Disadvantages
 - To maximize window of fetal exposure, the entire quantity of meconium is essential.
 - Meconium is a HETEROGENEOUS material that is not subjected to mixing in the fetal intestine
 - If cannot obtain the entire meconium then minimum of 2g required – up to 22% of specimens are rejected due to insufficient quantity
 - Contamination with urine or transitional stool



Maternal Hair

Provides a detailed record of gestational drug use.

9 cm should provide a detailed account of drug use throughout pregnancy

False positive results associated with passive drug exposure

Need approximately 200 stands

Requires technical expertise - limited centers to analyze

Neonatal Hair

Indicates exposure during the third trimester

0.5 inch corresponds to about 30 days of gestation.

Comparable sensitivities to meconium

Neonates have little hair

Difficult to obtain a sample

Umbilical Cord

- D. Montgomery, *et al.* (2006) were the first to compare the efficacy of umbilical cord tissue to meconium in detecting drug abuse during pregnancy.
 - 118 paired samples of umbilical cord specimens and meconium were analyzed
 - Agreement between umbilical cord and meconium samples was greater than 90% for amphetamines, cocaine, opiates and cannabinoids

Multicenter trial – 2008 D Montgomery, et al.

Confirmed the feasibility of using umbilical cord tissue to determine drug abuse during pregnancy.

- Negative Predictive Value >98%
 - If no drug is detected in the sample, assurance is high that none of the drugs tested for were in the sample.
- Positive Predictive Value 70-95%
 - If drug is detected in the sample, assurance is high that the drug was in the sample
 - Positive predictive values increased to nearly 100% if positive samples were retested using mass spectrometric methods

Umbilical Cord

- Commercial drug screening on umbilical cord tissue has been available in the United States since October 2007.
- 4 drug screening panels are available
 - 5 drug panel
 - 7 drug panel
 - 9 drug panel
 - 12 drug panel
 - EtOH testing is also available

5 Drugs	7 Drugs	9 Drugs	12 Drugs
Amphetamines	Amphetamines	Amphetamines	Amphetamines
Cannabinoids	Cannabinoids	Cannabinoids	Cannabinoids
Cocaine	Cocaine	Cocaine	Cocaine
Opiates	Opiates	Opiates	Opiates
PCP	PCP	PCP	PCP
	Methadone	Methadone	Methadone
	Barbituates	Barbituates	Barbituates
		Benzodiazepines	Benzodiazepines
		Propoxyphene	Propoxyphene
			Meperidine
			Oxycodone
			Tramadol

Umbilical Cord

- 5 Drug Screen - \$149
 - 5 Drug Screen + ETOH - \$209
- 7 Drug Screen - \$169
 - 7 Drug Screen + ETOH - \$229
- 9 Drug Screen - \$189
 - 9 Drug Screen + ETOH - \$249
- 12 Drug Screen - \$209
 - 12 Drug Screen + ETOH - \$269

Urine

- 5 Drug Screen - \$32

Hair

- 5 Drug Screen - \$95

Meconium

- 5 Drug Screen - \$50

Exposure During Pregnancy



The Placenta and Drugs of Abuse

- Illicit substances, prescription opiates and benzodiazepines are highly lipophilic and of a relatively low molecular weight
- Not filtered by the placenta and pass readily from the maternal circulation to the fetal circulation

Implications for the Fetus

- Once a drug crosses the placenta it accumulates in the fetus
 - Developmental deficiencies of the enzymes required for glucuronidation and oxidation delay metabolism of the drug.
 - Renal immaturity delays the excretion of the drug once it is metabolized

Classic Neonatal Drug Withdrawal

- 60-80% of neonates exposed in utero to opiates will develop signs and symptoms of withdrawal
- Opioid exposed infants demonstrate a high rate of perinatal morbidity and mortality

Heroin

Synthesized from morphine

- Usually appears as a white or brown powder or as a black sticky substance, known as “black tar heroin.”
- Can be injected, inhaled by snorting or sniffing, or smoked
 - All three routes of administration deliver the drug to the brain very rapidly
- Nearly half of young people who inject heroin surveyed in three recent studies reported abusing prescription opioids before starting to use heroin.



Heroin



Heroin use during pregnancy is associated with increased fetal morbidity and mortality including:

- Growth Restriction
- Placental Insufficiency
- Preeclampsia
- Premature rupture of membranes

Zohydro ER

1st

Oral, Extended Release
Hydrocodone without
Acetaminophen for Treating
Chronic Pain

PDUFA Date March 1, 2013



Extended release hydrocodone

- Indicated for the management of pain severe enough to require daily around the clock long-term opioid treatment for which alternative treatment options are inadequate
- Only for patients who are opioid tolerant
- Crushing chewing or dissolving the capsules can lead to uncontrolled delivery
- Approximately 5x more potent than oxycontin



- *Mitragyna speciosa*
- A 4 to 16 meter high tropical tree indigenous to South East Asia, the Philippines and New Guinea but now cultivated elsewhere.
- Kratom is in the same family as the coffee tree

The Different Faces of Kratom

- Crushed/powdered dried leaves (light to dark green)
- Powdery, greenish or beige-brown kratom
 - Fortified with extracts from other leaves
- Paste-like extracts and dark brown kratom resin
 - Made by partially or fully boiling down the water from aqueous kratom leaf suspensions
- Tinctures and capsules, filled with powdered kratom



Kratom

- Traditionally, fresh or dried leaves are chewed or made into tea; they are seldom smoked
- Stimulant effects at low doses
- Sedative, narcotic and euphoric effects at high dosages
 - Effects occur within 5 to 10 minutes after ingestion and last for 2 to 5 hours
 - Used in traditional medicine and as an opium substitute

Kratom

- Large, sedating doses (10–25 g) of dried leaves
- Initially may produce sweating, dizziness, nausea and dysphoria
- These effects are shortly superseded with calmness, euphoria and a dreamlike state that last for up to six hours.

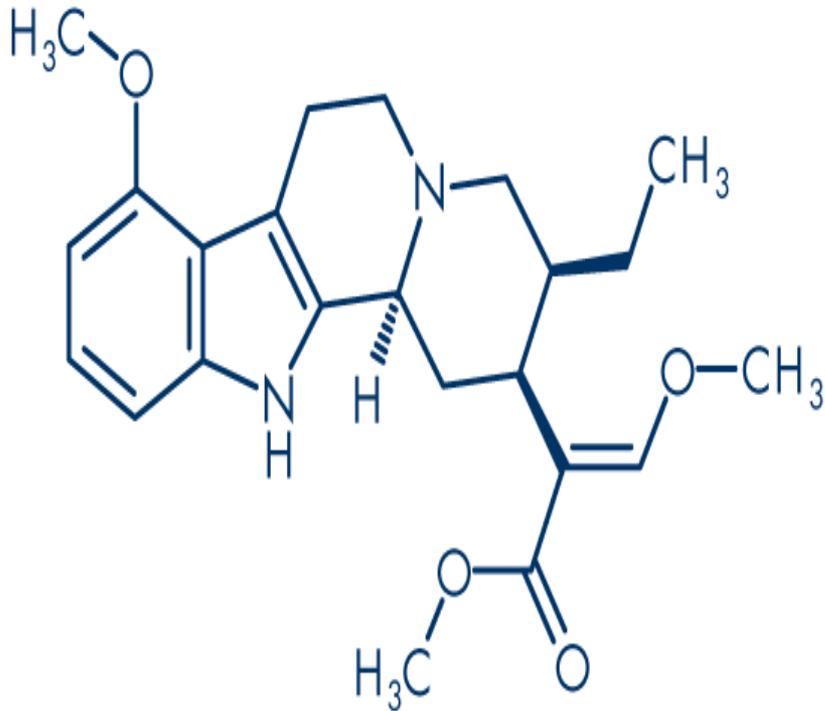
Kratom

- Regular use may produce dependence.
 - The withdrawal symptoms in humans are relatively mild and typically diminish within a week.
 - Craving, weakness and lethargy, anxiety, restlessness, rhinorrhea, myalgia, nausea, sweating, muscle pain, jerky movements of the limbs, tremor, sleep disturbances and hallucination
 - Can precipitate withdrawal symptoms in Neonates
-

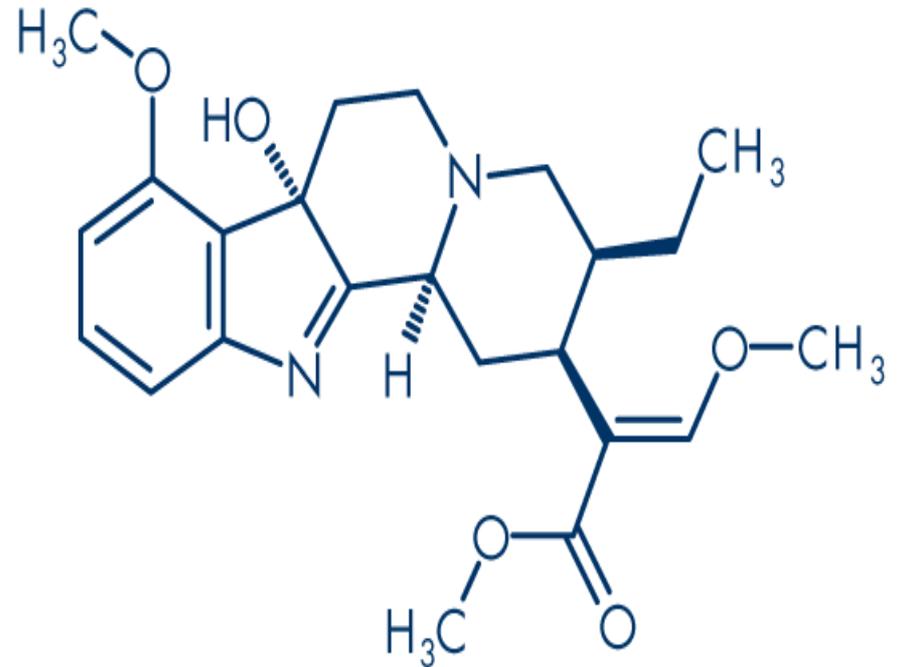
Kratom

- The phytochemicals isolated from various parts of the tree include over 40 structurally related alkaloids as well as several flavonoids, terpenoid saponins, polyphenols, and various glycosides.
 - The main psychoactive components in the leaves are:
 - Mitragynine and 7-hydroxymitragynine,
 - Both found only in *Mitragyna speciosa*.
-

Mitragynine



7-Hydroxymitragynine



Kratom

- Mitragynine and 7-hydroxymitragynine, are selective and full agonists of the μ -subtype opioid receptor.
- 5-HT_{2a} and postsynaptic α_2 adrenergic receptors, as well as neuronal Ca²⁺ channels are also involved in the unique pharmacological activity of mitragynine.

Kratom and Animal Studies

- Cough-suppressant effects of mitragynine were comparable to those of codeine
- The analgesic effect of 7-hydroxymitragynine was several times more potent than morphine
- Mice chronically treated with 7-hydroxymitragynine developed tolerance and cross-tolerance to morphine
- Withdrawal precipitated by naloxone administration

Kratom Tea



- Traditionally, the fresh or dried leaves of kratom are chewed or brewed into tea.
- Lemon juice is often added to facilitate the extraction of plant alkaloids
- Sugar or honey may be added to mask the bitter taste



Ketum Drinks

- Prepared by extended boiling of fresh leaves in water
- One 250 ml glass of 'ketum' contained 22.5–25 mg mitragynine
- About three such drinks a day are said to be sufficient to diminish opiate withdrawal symptoms

4x100

- Ice-cold cocktails made from:
 - Kratom leaves
 - Caffeine-containing soft drink
 - Codeine- or diphenhydramine-containing cough syrup
 - May also add anxiolytic, antidepressant or an analgesic drug



Kratom

- Is listed by DEA as a drug of concern
- Not scheduled under the Controlled Substances Act in the US.
- No legitimate medical use in the U.S.
- Widely available on the Internet.
- There are numerous vendors within and outside of the U.S.

Several countries in Europe, Australia, New Zealand, Malaysia, Myanmar and Thailand control Kratom under their narcotic laws





Acetyl Fentanyl

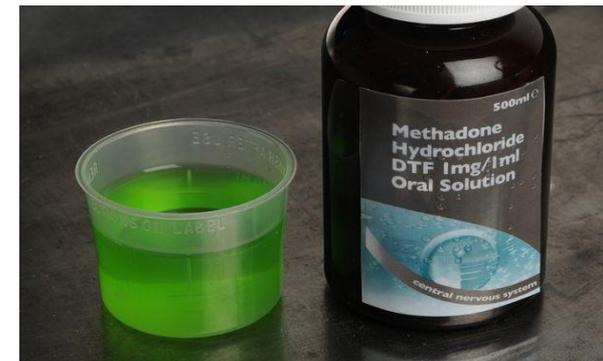
- Potent synthetic opiate
- Not a part of most illicit drug screens
 - ELISA does not differentiate fentanyl and acetyl fentanyl
 - Confirmatory analysis such as gas chromatography/mass spectrometry (GC/MS) is required to confirm the presence of acetyl fentanyl
- Not approved for medical use in the United States
- No published studies on safety for human use.

Acetyl Fentanyl

- May serve as a direct substitute for heroin or other μ -opioid receptor agonist substances in opioid dependent individuals
- Has been detected in tablets that mimic pharmaceutical opiate products, in powder form and spiked on blotter papers
- At least 52 confirmed fatalities involving acetyl fentanyl in the United States in 2013-2015
- Schedule I Substance as of May 2015

Methadone and Buprenorphine

- Used in an attempt to minimize the poor outcomes associated with illicit opiate use
 - Improved birth weight and decreased other risks of IV drug abuse
 - 2.5 fold increase in the rate of preterm birth in methadone exposed fetuses



Maternal dose of Methadone

- A higher dose in the third trimester, is associated with longer neonatal hospital stays.
- For every 5.5mg increase in methadone dose during pregnancy, neonatal length of stay (LOS) increased by 1 day.
- The duration of drug exposure in utero is an additional factor that dictates severity

Maternal Dose of Methadone

- Liu et al found that a combination of higher dose before delivery and longer gestational age was associated with NAS treatment, and infants with longer gestation have increased LOS compared with those born with shorter gestation (<36wk).
 - Some of this is due to innate difference in preterm and term infants

Maternal Dose of Methadone

- Longer gestation contributes to NAS severity due to the high permeability of the placental barrier during the third trimester that results in increased levels of fetal methadone exposure nearing delivery.
- There are also genetic contributions to need for postnatal pharmacological treatment.
 - Single nucleotide polymorphisms of the m-opioid receptor (OPRM1, variant A11AG) and catecholomethyltransferase (COMT) genes.

Methadone and Buprenorphine

Significant duration of drug withdrawal

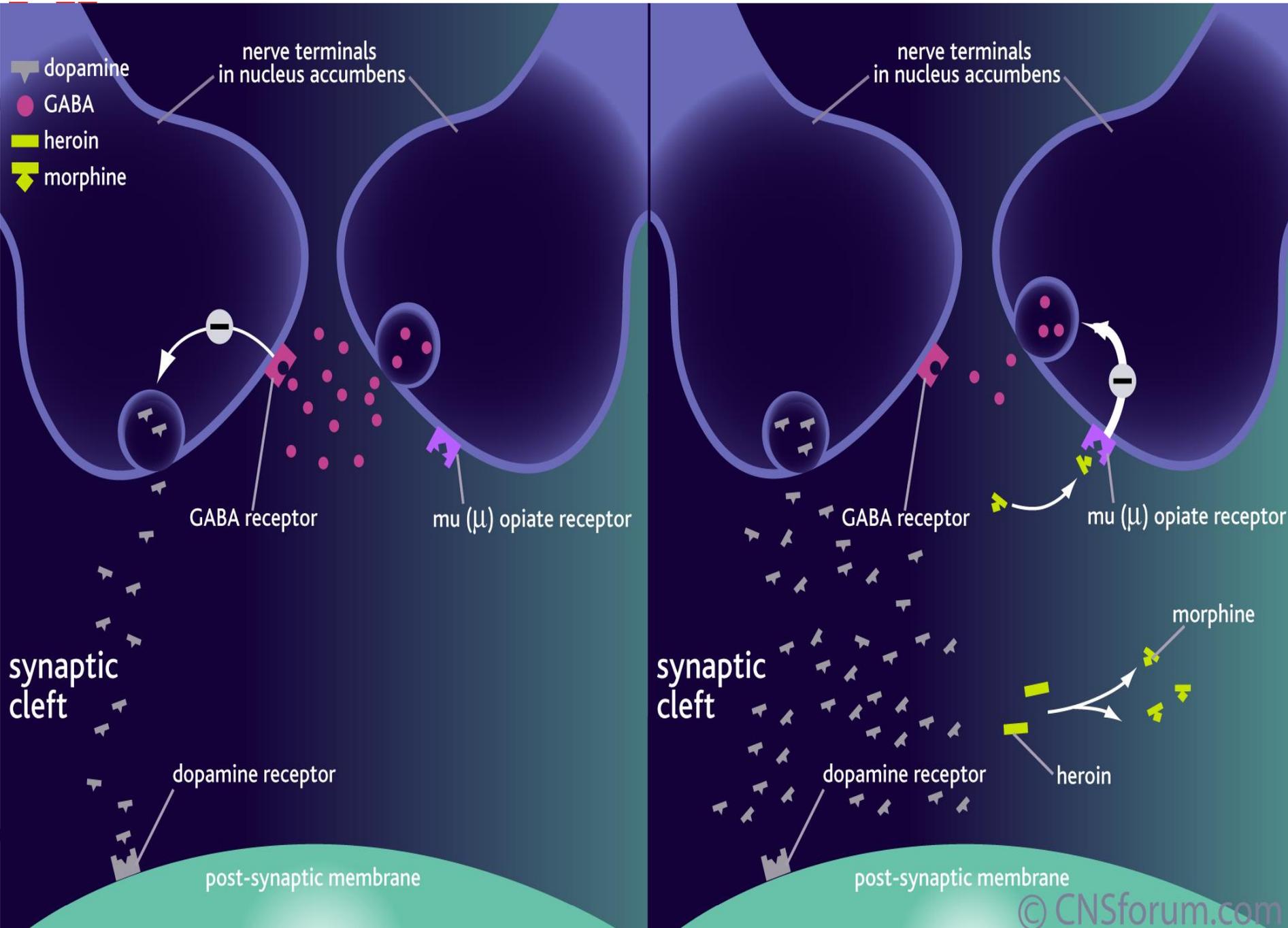
- **MOTHERS Study**
 - Buprenorphine maintenance during pregnancy was associated with a decreased need for morphine treatment in the neonate and decreased neonatal length of stay when compared with the use maternal methadone

Mechanism of NAS

- Multifactorial and poorly understood
- Impact of opioid exposure on the development of the fetus is unclear
- Effect on the developing brain is typically functional and therefore may not be detected at birth but are seen later in childhood, adolescence or adulthood

When opiates bind to the opiate receptors they change the shape of the nerve ending.

- Prevents acetylcholine release and thus pain transmission to the brain
 - Decreases GABA release
 - Increases dopamine release which contributes to the sense of pleasure/well being
-



Chronic Stimulation of Opioid Receptors

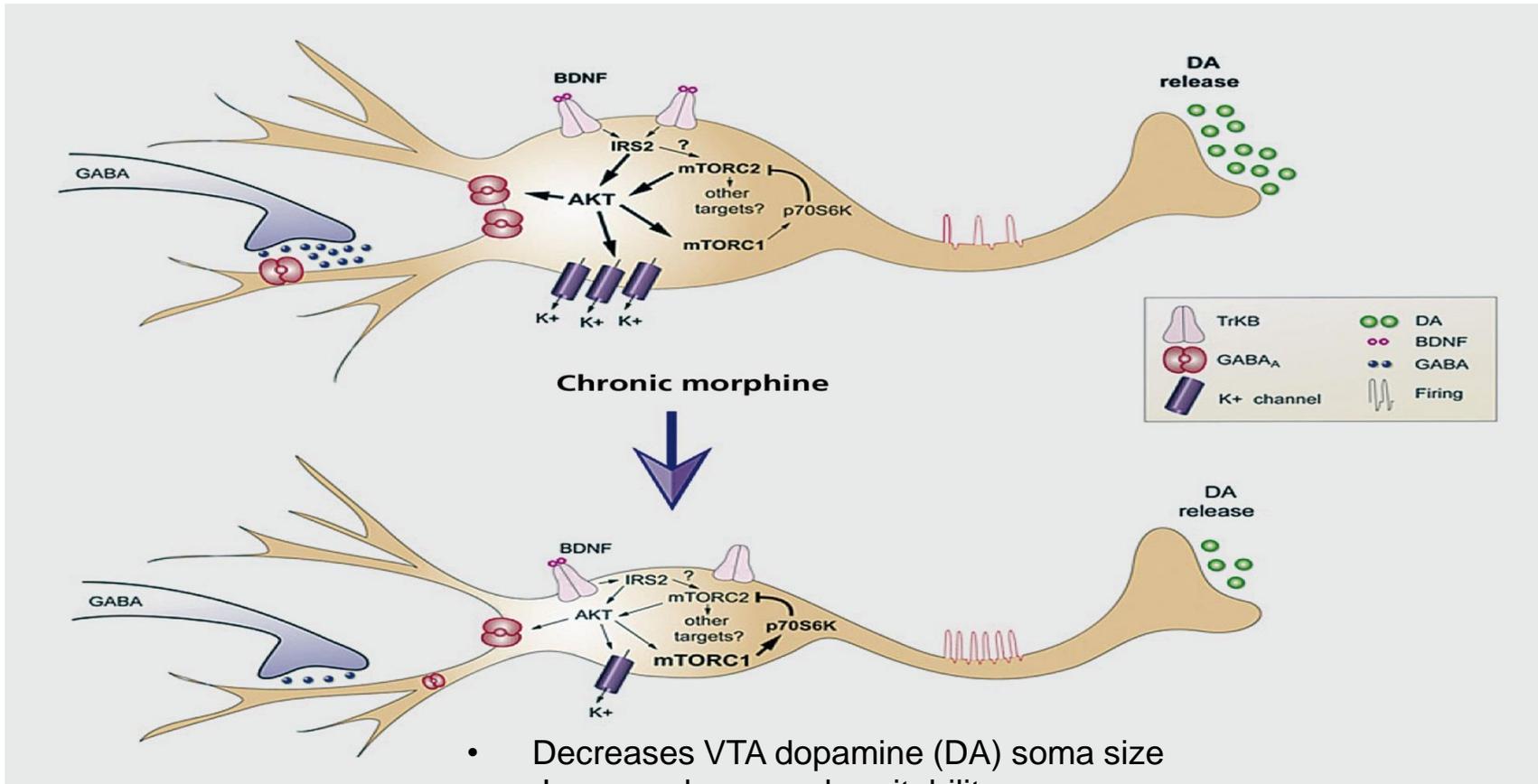
Aberrant synaptic plasticity

- Inability of the synapse between two neurons to change in response strength to either use or disuse of synaptic pathways.
- Activation of NMDA receptor channels which contributes to dependency

Alteration of the number of receptors located on a synapse.

Inhibition of adenylate cyclase

Inappropriate dopamine release



- Decreases VTA dopamine (DA) soma size
- Increased neuronal excitability
- Dopamine transmission decreased
- The net effect of morphine is a less responsive reward pathway, ie, reward tolerance.

Withdrawal from Opiates

- Down regulation of the μ opioid receptors
 - Inadequate production of dopamine and endogenous endorphins
- Increased GABA Release
 - Rapid and marked decrease in dopamine release in the neuronal synapses
- Sympathetic Hyperactivity
 - Up-regulation of the Locus Ceruleus due to elevated cAMP

Assessing the Severity of Withdrawal

- The tools available for evaluating the severity of withdrawal and need for pharmacological treatment are observer rated scales
- The Finnegan Scale and Lipsitz Tool are the most commonly used scales.

Finnegan Scale/Modified Finnegan Scale

- Most commonly used scoring systems
- Created to assess the severity of disease in infants with known opiate exposure
- On day of life 2 a score of 7 corresponds with the 95th percentile for non-exposed infants
 - Score of 8 or greater is highly suggestive of in utero opioid exposure

Finnegan Scoring System

- Weighted scoring of 21 signs and symptoms of withdrawal
- Developed for term infants

SYSTEMS	SIGNS AND SYMPTOMS	SCORE
CENTRAL NERVOUS SYSTEM DISTURBANCES	High Pitched Cry	2
	Continuous High Pitched Cry	3
	Sleeps < 1 Hour After Feeding	3
	Sleeps < 2 Hours After Feeding	2
	Hyperactive Moro Reflex	2
	Markedly Hyperactive Moro Reflex	3
	Mild Tremors Disturbed	2
	Moderate Severe Tremors Disturbed	3
	Mild Tremors Undisturbed	1
	Moderate Severe Tremors Undisturbed	2
	Increased Muscle Tone	2
	Excoriation (specify area): _____	1
	Myoclonic Jerks	3
Generalized Convulsions	3	
METABOLIC VASOMOTOR/ RESPIRATORY DISTURBANCES	Sweating	1
	Fever < 101 ^o F (39.3 ^o C)	1
	Fever > 101 ^o F (39.3 ^o C)	2
	Frequent Yawning (> 3-4 times/interval)	1
	Mottling	1
	Nasal Stuffiness	1
	Sneezing (> 3-4 times/interval)	1
	Nasal Flaring	2
	Respiratory Rate > 60/min	1
	Respiration Rate > 60/min with Retractions	2
GASTROINTESTINAL DISTURBANCES	Excessive Sucking	1
	Poor Feeding	2
	Regurgitation	2
	Projectile Vomiting	3
	Loose Stools Watery Stools	2 3
SUMMARY	TOTAL SCORE	
	SCORER'S INITIALS	

Assessing the Severity of Withdrawal

Observer-rated scales are an essential component in the assessment and treatment of neonatal drug withdrawal but they do have some shortcomings

- Lack of rigorous psychometric testing to establish reliability and validity
- Lengthy training and administration times
- Subjective

We need more objective, well studied diagnostic tools to assess the severity of drug withdrawal.

Ideal Treatment Regimen

A protocol driven approach which incorporates symptomatic care and a drug titration schedule to control symptoms

Goal of Treatment

- Use symptomatic and pharmacologic therapies
 - Ensure proper feeding and growth
 - Facilitate appropriate development
 - Foster the maternal-infant bond
 - Prevent neurologic sequelae

- Not to prevent withdrawal

Symptomatic Care

- Forty percent of infants withdrawing from opiates will only need symptomatic care
 - Tightly swaddling
 - Holding
 - Rocking
 - Environmental Control
- Withdrawal scores less than eight

Initiation Pharmacologic Therapy

- Based on Finnegan scores:
 - 3 consecutive scores of 8 or greater
 - 2 consecutive scores of 12 or greater
- No definitive evidence to determine most effective starting score

Pharmacologic Therapy

The American Academy of Pediatrics and experts in the field have identified opioid replacement as the first line therapy for withdrawal symptoms after in utero exposure to opiates

Opioid Replacement

- Improves weight gain but lengthens hospitalization when compared to symptomatic care
- High quality data on the safety and efficacy of specific opioids and the optimal dosing regimens are lacking

Morphine

- Most commonly used opioid for replacement therapy
 - Physiologic Replacement
 - Controls all of the symptoms of withdrawal
 - Preservative Free Solution
 - Potent analgesic properties and has high addictive potential

Morphine

- Pharmacodynamics in the neonate are affected by:
 - Immature metabolic enzymes, and renal function
 - Changes in fat and extracellular fluid balance during the neonatal period
- Pharmacokinetics of orally administered morphine in the neonate are not fully understood

Methadone

- Long acting synthetic opioid
 - Less flux between peak and trough levels
 - Ease of administration
 - Difficult to wean
- Oral formulation contains 8% ethanol

Methadone

- Pharmacokinetic modeling in the neonate suggests significant inter-patient and developmental variability
- Absorption, distribution, metabolism and excretion of methadone are impacted by:
 - Gestational age of the infant
 - Body adiposity
 - Pharmacogenetics
 - Disease states

Methadone

- Individualized dosing and tapering schedules should be used to control symptoms
 - Titrate dose to effect
 - Max 10mg/day
- Tapering dose by 10-20% per wk. over 1 to 1.5 months

Methadone

- The elimination half life is significantly longer than its duration of analgesic action
 - Respiratory depressant effects of methadone occur later and persist longer than its peak analgesic effects
- Prolonged QT syndrome and torsades de pointes
 - Baseline EKG to assess QT interval prior to the initiation of therapy and then intermittent monitoring

Adjunct Therapy - Phenobarbital

- Allows for a lower doses of opiates.
- Side effects – especially at higher doses
 - Sedation
 - Poor Sucking
- It does not control diarrhea that occurs with withdrawal.
- The elixir contains 20% alcohol.
- IV solution 5% alcohol 60% polyethylene glycol

Adjunct Therapy - Clonidine

- Alpha II Receptor Agonist
 - Decreases sympathetic outflow through the activation of inhibitory neurons
-

Clonidine

- A multicenter randomized, double blinded clinical trial conducted in 2009 found that clonidine in combination with DTO stabilized and detoxified infants with moderate to severe drug withdrawal more rapidly than DTO alone.
- No adverse cardiovascular effects
- Further studies are needed to determine long-term safety

Clonidine vs. Phenobarbital

- A prospective non-blinded block randomized controlled trial that compared the efficacy of clonidine vs. Phenobarbital in reducing neonatal morphine sulfate therapy days for NAS.
 - 68 infant were randomize to 1 of 2 study arms; adjunctive therapy with either clonidine or Phenobarbital.

Clonidine vs. Phenobarbital

- Phenobarbital or clonidine was started at the same time morphine was initiated.
- They found that for both groups the length of treatment was improved verses the length of stay prior to study implementation.

Clonidine vs. Phenobarbital

- The infants on Phenobarbital had a 4.5 day decrease in the length of morphine therapy but were discharged home on Phenobarbital.
 - Stayed on this medication for 1-8 months with a mean of 3.8 months.
 - Six of the infants in Phenobarbital group were lost to follow-up after discharge.

Clonidine vs. Phenobarbital

- The overall length of NAS treatment was shorter with the clonidine group and no outpatient therapy was required
- Infants were on morphine sulfate for a longer period of time.

Clonidine

- Short and long term side effects have not been well studied in neonates
- Been used in adults and children for years
- CV side effects do not seem to be an issue at NAS dosing

Phenobarbital

- Animal studies suggest inhibited neurogenesis and survival with long term Phenobarbital use.
- Human Studies show neurodevelopmental and behavioral compromises with long term therapy.

Breastfeeding and NAS



WHO and AAP

Recommend that infants should be exclusively breastfed for the first 6 months of life to achieve optimal health and development



AAP - Breastfeeding and Illicit Drug Use

- The use of marijuana, illicit opiates, cocaine, methamphetamine and other street drugs is a contraindication to breastfeeding.
- For most street drugs the risks to the infant of ongoing active use by the mother outweigh the benefits of breastfeeding.
 - The doses of the drug and the contaminants within the drug are unknown.

AAP - Breastfeeding and Illicit Drug Use

- Marijuana, cocaine, opiates and methamphetamines have an affinity for lipids and accumulate in human milk
 - Marijuana has been shown to alter brain neurotransmitters as well as brain biochemistry, resulting in decreased protein, nucleic acid, and lipid synthesis.
 - What does this do to a developing brain??

Breastfeeding & Medication Assisted Treatment

- Supervised methadone and buprenorphine use is compatible with breast feeding
 - No other drugs of abuse on routine toxicology screens
 - Ingestion of maternal breast milk can decrease the severity of withdrawal
 - The magnitude of response is correlated with volume of MBM ingested
 - The transmission of methadone in the breast milk could be as high as 0.05mg/kg/day

Table 1 Characteristics of the clinical studies retrieved by the systematic search strategy

Citation	Study group	Study type (level of evidence)	Outcome	Key result	
Wachman <i>et al</i> ¹	38 breastfed and 48 formula-fed infants of mothers using methadone or buprenorphine during pregnancy	Prospective cohort study (2b)	Effect of breastfeeding on LOS (primary outcome), maximum Finnegan score, maximum dose and need for pharmacological NAS treatment	Breastfeeding shortened the LOS (15.8 vs 27.4 days; $p < 0.001$) and decreased the need for pharmacological treatment (50% vs 77%, $p = 0.009$)	Multicentre study with possible variability in scoring, treatment and weaning methods between centres
Welle-Strand <i>et al</i> ²	58 breastfed and 20 formula-fed infants of mothers using methadone and 37 breastfed and 9 formula-fed infants of mothers using buprenorphine during pregnancy	Retrospective and prospective cohort study (3b)	Effect of breastfeeding on incidence and duration of NAS	Incidence of NAS: 53% of breastfed infants, 80% of formula fed ($p < 0.05$) Duration of NAS treatment in breastfed infants 31 vs 48.9 days in formula fed infants ($p < 0.05$)	Small sample sizes and a multicentre study with variability between centres in experience in evaluation and treatment of NAS
Pritham <i>et al</i> ³	14 breastfed infants and 96 formula-fed infants of mothers using methadone during pregnancy.	Retrospective cohort study (3b)	Effect of breastfeeding on length of hospital stay (LOS) of the exposed newborn.	Breastfeeding shortened the LOS by 3.3 days ($p = 0.05$)	Finding is just not statistically significant probably due to the small sample size of the breastfeeding group
Jansson <i>et al</i> ⁴	8 breastfed infants and 8 formula-fed infants of mothers using methadone during pregnancy.	Prospective case-control study (3b)	Effect of breastfeeding on neurobehavioral outcome and need of pharmacological treatment for NAS	No significant effect on infant neurobehaviour or need for pharmacotherapy for NAS.	Small sample size due to strict inclusion and exclusion criteria
Abdel-Latif <i>et al</i> ⁵	85 breastfed infants and 105 formula-fed infants of opioid dependent mothers	Retrospective cohort study (3b)	Effect of breastfeeding on frequency and severity of NAS	Breast fed infants less pharmacological treatment for withdrawal (52.9% vs 79%)	Not merely methadone-exposed infants, also other drugs

NAS, neonatal abstinence syndrome.

Clinical Studies to Date

- No randomized controlled studies
- Most are observational studies
 - Introduce bias
- The differences in how outcomes were measured makes direct comparisons impossible

Study Findings

- Infant who received MBM appeared to require less pharmacologic therapy and spent a shorter time in the hospital
- These findings may be due to confounders
 - Less psychological comorbidity
 - Better adherence to supervised treatment program
 - More supportive staff attitudes towards mother and infant dyad who breastfeed vs. those who bottle feed

Study Findings

- All studies suggest that breastfeeding (in mothers on methadone or buprenorphine) is associated with:
 - Reduction in severity
 - Decreased need for pharmacologic therapy
 - Decreased length of hospitalization

Breast feeding and/or provision of expressed breast milk should be encouraged unless there is a clear contraindication

HIV and/or illicit drugs of abuse



Additional Thoughts on Breastfeeding

- The infant must be able to gain appropriate weight.
- Breast milk does not induce clinically important sedation
- Abrupt cessation and/or rapid weaning of maternal breast milk can precipitate rebound withdrawal.
- Close postpartum follow-up of the mother and infant are essential



Kentucky Statistics for Child Maltreatment

- 69.7% of childhood fatalities and near fatalities as a result of child maltreatment between 2010 and 2014 were associated with caregiver substance abuse
 - Children less than 1 year of age account for the largest group
 - Domestic Violence was noted in 68.7% of cases
 - Opiate and other prescription drugs were commonly found in the affected homes

Kentucky Statistics for Child Maltreatment

- Since January 2014 the department has the ability to distinguish if drug abuse is:
 - Present in the home
 - Indirectly contributed to the incidence
 - Directly contributed to the incidence

Follow-Up

A safe, stable and nurturing home environment is essential during the early years of brain development to address the stress of early adverse experiences

Follow-Up

- Infants who have been identified as having been drug exposed in utero need a pediatric medical home in which they can easily receive
 - Regular growth and nutritional assessments
 - Evaluation for developmental and social/emotional delays
 - Close follow-up for subtle signs of neglect and abuse

Quality Improvement Efforts

The Governor's Summit on Infant Mortality in 2013
sited improved care for infants and mothers with
perinatal drug exposure as a priority for the state of
Kentucky

Initiation of Pharm tx:

3 Consecutive scores ≥ 8
or
2 consecutive scores ≥ 12

Begin tx with
Oral Morphine
0.05mg/kg/dose

Escalating:

If consecutive scores are still
 $\geq 8 \times 3$ or $\geq 12 \times 2$
Increase Morphine dose by
25% for elevated
consecutive scores until you
reach a dose of
0.13mg/kg/dose

Then if consecutive scores are still $\geq 8 \times 3$,
or $\geq 12 \times 2$ start
Clonidine 1 mcg/kg/dose q 3hrs

**BP should be obtained every 8 hours
while on Clonidine**

If consecutive scores remain $\geq 8 \times 3$, or $\geq 12 \times 2$
Increase morphine by 25%
If consecutive scores remain $\geq 8 \times 3$, or $\geq 12 \times 2$
Increase Clonidine to 1.5mcg/kg
If consecutive scores remain $\geq 8 \times 3$, or $\geq 12 \times 2$
**Continue to increase Morphine by 25% until the
infant is captured**
Max Dose 0.25mg/kg/dose q 3hrs

Then if consecutive scores are still $\geq 8 \times 3$,
or $\geq 12 \times 2$
Add third line drug:
Phenobarbital 2.5 mg/kg/dose q 12hrs

Weaning:

If scores $< 8 \times 24$ hours
wean Morphine

* Scores ≤ 6 , wean Morphine by 10-15% q 24 hrs
* Scores greater than 6 but ≤ 8 , wean by 10-15% q 48-72hrs
* 3 Scores in 24hrs ≥ 8 , do not wean (Consider increasing dose or adding an additional drug if consecutive scores $> 12 \times 2$ during weaning process)

Discontinue Morphine at a dose of
0.02mg q3 hrs and scores < 8

Weaning Clonidine:

*If dose is 1.5mcg/kg/dose q 3hr then wean to 1mcg/kg/dose q 3hr
*In 24 hours wean to q 6hrs if scores ≤ 8
*Monitor BP's every 8 hours
*May D/C Clonidine once stable for 24-48hrs on Q6.
*Monitor for at least 48hrs off Clonidine to assure no rebound hypertension

Weaning Phenobarbital:

*Wean by 25% if dose is larger than 2.5 mg/kg/dose q 12hrs until you reach 2.5mg/kg dose q 12hrs then D/C
*D/C Phenobarbital at 2.5mg/kg/dose
*Monitor for at least 48 hrs off Phenobarbital to assure stability before discharge.

Please call the on-call person:

If 3 scores are consecutively ≥ 8 (when trying to capture infant)

If 2 scores are consecutively ≥ 12

If pt. has started the weaning process: 2 consecutive scores ≥ 12 is criteria for increasing doses and/or starting additional meds

What we have learned to date:

- NAS is 3 letter acronym that will be a permanent part of the practice of pediatrics.
 - Robust objective assessment tools and treatment regimens are needed to drive quality improvement and improve patient care
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