Opiates: Concepts and Controversies

Fetal Exposure to Noxious Substances
Neonatal Abstinence Syndrome

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Neonatal Abstinence Syndrome (NAS)

Generalized multi-system disorder associated with a constellation of typical signs and symptoms of withdrawal in infants exposed during fetal life to opioids, certain illicit drugs or prescription medications to which they have developed dependence and tolerance.
NAS

- Addiction
- Dependence
- Tolerance

We never say a baby is addicted!
ADDICTION

- Chronic disorder
- Compulsive drug seeking or drug consuming behavior
- Inability to control craving
- Negative consequences (social, economic, psychologic)
DEPENDENCE

Requirement of the continuous presence of a drug to maintain normal cellular function
TOLERANCE

Progressive requirement for greater concentration of a drug to achieve the same pharmacologic effect.
Gestational Exposure to Drugs of Abuse

“Largest, Preventable cause of environmentally induced Developmental Delay in Infants”

Malagna et al : Clinics in Perinatology, 1999
Of all substances of abuse (cocaine, amphetamines, marijuana, opiates, benzos)

**alcohol**
causes the most serious effects in the fetus
Most severe and consistent physical malformations occur during the first trimester. 2\textsuperscript{nd} Trimester exposure is associated more with IUGR, Spontaneous Abortions.
Maternal Treatment Goals:

- Prevent and treat STD’s inc. HIV, Hep.B & C, Syphilis, GC, Herpes
- Prevent preterm labor, Prematurity, IUGR, Developmental delay
- Prevent CNS injury of the developing fetal brain
- Decrease incidence of SIDS
Methadone and Buprenorphine

- Numerous studies over many years show that both agents
  - Keep patients in treatment
  - Reduce illicit opioid use
  - Reduce morbidity and mortality
- Methadone may have a slight advantage in efficacy
- Buprenorphine has a safety advantage but may require more skill and experience for induction
Buprenorphine

- Buprenorphine may produce less severe NAS and fewer neurobehavioral problems ([Coyle et al, 2012](#)),
- Higher birthweight, and larger head circumference compared with methadone ([Welle-Strand et al, 2013](#)).
- Several studies have found no difference in growth patterns between buprenorphine-exposed and non-exposed neonates ([Bakstad et al, 2009](#); [Fischer et al, 2000](#); [Schindler et al, 2003](#); [Sundelin Wahlsten and Sarman, 2013](#)).
Drugs that cause Dependence and NAS

- **Opiates**
  - Opium
  - Codeine
  - Morphine
  - Heroin

- **Opioids**
  - Fentanyl
  - Demerol (Meperidine)
  - Oxycodone
  - Percodan / Percocet
  - Darvon, Lomotil
  - Buprenorphine (Subutex)
  - Methadone
“Opium Poppy”

**Papaver Somniferum**

Somnus  
(Roman God of Sleep)

**Hypnos**  
(Greek God of Sleep)

**Thanatos**  
(Greek God of Death)

**Morpheous**  
Son of Hypnos  
God of Dreams
Drugs that cause Dependence and NAS

- Alcohol

- Benzodiazepine & Derivatives
  - Valium; Librium; Xanax
  - Placidyl; Ativan; Versed

- Barbiturates
  - Fiorinal; Nembutal; Seconal
  - Phenobarb; Black Beauties
Drugs of Abuse

- Low Molecular Wt.
- Highly Lipophilic
- Easily Cross the Placenta
- Rapid equilibration of drug between mother and fetus
- Act by binding to μ & κ receptors and mimicking the action of or changing the activity of endogenous neurotransmitters
- May cause Fetal Dependence
Drugs of Abuse

- Accumulate in the fetus
  - ↓↓ Metabolism
  - ↓↓ Renal function
  - ↓↓ Enzymitic activity

- Potentially Teratogenic
  - Time of exposure
  - Dose / Severity of exposure
  - Duration of exposure
Brain Development and FENS

- Neurotransmitters play a major role in brain development.
- Capable of inducing and sustaining growth and differentiation of neural systems.
- **Interfering** with normal required neurotransmitter signals may lead to structural changes in the brain.
- May prevent the brain from going through its normal developmental process.
- Changes in brain architecture, growth, function, and behavior.
Brain development and FENS

- In vivo animal studies
- Alterations in fetal brain development seen with
  - Opiates- Changes in density of neurons and morphology; Less neuronal processes; Alteration of neuronal myelination; Interferes with neuronal differentiation as well as μ-opioid receptor (MOR) expression in mice; may promote apoptosis of neurons via mu receptors.
  - Cocaine- Reduction of brain growth
    - Deficits in neuronal differentiation and migration
  - Alcohol- Changes in distribution of neuronal processes;
    - Disruption of cytoarchitecture; Major malformations
### Effects of Prenatal Drug Exposure
#### Short Term Effects and Birth Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Nicotine</th>
<th>EtOH</th>
<th>MJ</th>
<th>Opiates</th>
<th>Cocaine</th>
<th>Meth...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal Growth</strong></td>
<td>Effect</td>
<td>Strong Effect</td>
<td>?No? Effect</td>
<td>Effect</td>
<td>Effect</td>
<td>Effect</td>
</tr>
<tr>
<td><strong>Anomalies</strong></td>
<td>No Consensus</td>
<td>Strong Effect</td>
<td>No Effect</td>
<td>No Effect</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
<td>No Effect</td>
<td>Effect</td>
<td>No Effect</td>
<td>Strong Effect</td>
<td>No Effect</td>
<td>****</td>
</tr>
<tr>
<td><strong>Neuro-behavior</strong></td>
<td>Effect</td>
<td>Effect</td>
<td>Effect</td>
<td>Effect</td>
<td>Effect</td>
<td>Effect</td>
</tr>
</tbody>
</table>

*Pediatrics, March 2013*
# Effects of Prenatal Drug Exposure
## Long Term Effects

<table>
<thead>
<tr>
<th></th>
<th>Nicotine</th>
<th>EtOH</th>
<th>MJ</th>
<th>Opiates</th>
<th>Cocaine</th>
<th>Meth</th>
</tr>
</thead>
</table>
| **Growth**     | No Consensus
| Strong Effect  | No Effect  | No Effect | No Consensus | **        |
| **Behavior**   | Effect                  | Strong Effect | Effect | Effect ? | Effect  | **        |
| **Cognition**  | Effect                  | Strong Effect | Effect | No Consensus | Effect  | **        |
| **Language**   | Effect                  | Effect | No Effect | **       | Effect  | **        |
| **Achievement**| Effect                  | Strong Effect | Effect | **       | No Consensus | **   |
Long term outcomes
Opiate exposure

- Infants who experienced NAS appear to be more vulnerable to the adverse effects of an impoverished environment.
Drugs that do not cause neonatal dependence

- Nicotine
- Cannabinoids
- SSRI Antidepressants
- Amphetamines
- Cocaine
- Bath Salts
## Signs and Symptoms of NAS

- **Central Nervous System**
  - Tremors
  - Increased Muscle Tone
  - Hyperreflexia
  - High Pitch Cry
  - Poor Sleeping
  - Restlessness
  - Seizures

- **Metabolic & Vasomotor**
  - Tachypnea
  - Fever and sweating
  - Mottling
  - Sneezing

- **Gastrointestinal**
  - Excessive sucking/rooting
  - Poor feeding
  - Spitting/Vomiting
  - Loose or watery stools
Neonatal abstinence

- 60-90% of term infants prenatally exposed to narcotics will develop NAS
- Infants < 33 wks rarely develop NAS
- Infants whose mother’s received < 30 mg methadone/day tend not to develop NAS
Neonatal abstinence
Risk Factors for Increase Severity of NAS

- Term
- Polydrug abuse
- Combination with benzodiazepines
- Specific gene polymorphisms of the \(-\)-opioid receptor (OPRM1) and catechol-O-methyltransferase (COMT)
- Smoking
- Methadone
- Combination with SSRIs
Neonatal Abstinence: Seizures

- Clinical Seizures 2% -10% of infants with NAS
- Abnormal EEG >30% of exposed infants without overt seizures
- Not related to methadone dose
- Mean age of onset – 10 days
- Tonic-Clonic or Rhythmic Myoclonic Jerks
- Prognosis is good with normal EEG in most infants at 1 yr. (depending on exposure)
- Phenobarbital does not prevent drug withdrawal induced seizures.
- Higher incidence of seizures with valium
Neonatal Abstinence: Seizures

E. Spitzmiller, Neonatology Today; Oct. 2013

- Use of aEEG to monitor sleep cycles and seizures in infants with NAS
- Small study with only 8 babies used in final analysis
- 88% of babies had electrographic seizures and altered sleep on aEEG
Long term significance?

Better control = Better long term outcomes?

Can use of aEEG improve outcomes?
Signs and Symptoms of NAS

- The GI findings may be the most severe
- Electrolyte imbalance & dehydration
- Up to 15% - 20% Wt. loss within 24-48 hrs.
Infants should be assessed for signs of withdrawal ½ to 1 hour after each feed. Infants will be scored in each of the 3 sections of the scoring chart. Allowances must be made for infants who are preterm or beyond the initial newborn period and for normal infant behavior.

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGN</th>
<th>SCORE</th>
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</thead>
<tbody>
<tr>
<td>C.N.S.</td>
<td>Excessive cry</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Continuous cry</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt;1hr after feed</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt;2hrs after feed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt;3hrs after feed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Over active Moro reflex</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very over active Moro reflex</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mild tremors disturbed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mod/severe tremors disturbed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild tremors undisturbed</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mod/severe tremors undisturbed</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Increased muscle tone</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Excoriation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Myoclonic jerks</td>
<td>3</td>
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<tr>
<td></td>
<td>Generalized convulsions</td>
<td>5</td>
</tr>
<tr>
<td>G.I.T.</td>
<td>Excessive Sucking</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Poor Feeding</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Regurgitation</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Loose stools</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Watery stools</td>
<td>3</td>
</tr>
<tr>
<td>OTHER</td>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fever 37.3 to 38.3 C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fever 38.4C and above</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Frequent yawning (&gt;3-4 in ½ hr)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sneezing (&gt;3-4 in ½ hr)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nasal Flaring</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Resp. rate &gt;60/min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Resp. rate &gt;60/min &amp; retractions</td>
<td>2</td>
</tr>
</tbody>
</table>

TOTAL SCORE

INITIALS

<table>
<thead>
<tr>
<th>PHARMACOLOGY</th>
<th>Rx</th>
<th>S</th>
<th>D</th>
<th>T</th>
<th>S</th>
<th>D</th>
<th>T</th>
<th>S</th>
<th>D</th>
<th>T</th>
<th>S</th>
<th>D</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Status; D-Dose; T-Time Coding: (+) Initiation (=) Maintenance (↑) Increase (↓) Decrease (—) Discontinuation</td>
<td></td>
<td></td>
<td></td>
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-- Modified from L.P. Finnegan (1986)
NAS
Finnegan Scoring System

- Quantitative measure of the symptoms of withdrawal
- Better objective assessment of the severity and progression of symptoms
- Standardization of management
  - When to start pharmacotherapy
  - When to start weaning
- Response to management strategies
Treatment of NAS
Supportive non-pharmacologic

- The cornerstone in the management of NAS
- Start before birth
- Continue throughout the infant’s hospitalization
- Provide mother with addiction and mental health support
Treatment of NAS
Supportive non-pharmacologic
Fresh Start Program

- Provides infant and mother with the best care coordination from pregnancy to years after birth
- Provides parents with strategies to better deal with attachment and emotional issues
- Helps develop a positive mother-baby relationship
- Provides mother with addiction and mental health support
Treatment of NAS
Supportive non-pharmacologic
Fresh Start Program

- Developmental follow up before and after discharge

- Goal is to prevent mother’s return to a normal lifestyle
  - Help mom and baby return home safely and healthy
  - Improve environment at home
  - Improve infant’s long term outcomes
  - Early detection and management of developmental issues
  - Prevent hospital readmissions
Treatment of NAS
Supportive non-pharmacologic

- 20-30% of ISAM are managed without medication
- Start as soon as possible after birth
- Provide a quiet, private environment and the option for nesting and avoid intensive care setting (Rooming-in)
- Close supervision by experienced personnel
- Perform constant evaluations of mother and infant, recognize problems, and institute the necessary interventions
- Nursing “TLC” Measures (to decrease sensory stim)  Pacifier for excessive sucking
  - Avoid loud music and noises
  - Frequent feedings and diaper changes
  - Hyper-caloric thickened formula
  - Swaddling/Swinging/Rocking/Positioning
- Environment: Quiet, dimly-lighted environment
  - Minimize alarms/beepers
Supportive non-pharmacologic Rx: Cuddler Program

- Important component of the developmental care
- Importance of human contact and touch has been well documented.
- Studies have shown that babies who are held more often may demonstrate greater growth and physiologic stability and may become more alert when awake.
- Cuddlers hold/rock/comfort infants on a daily basis.
Supportive non-pharmacologic Rx: Cuddler Program

**Neonatal Abstinence Syndrome (NAS) Babies**
Length of Stay (LOS) Outcomes for West Penn Hospital Pediatric Unit Cuddler Program 2009-2013

<table>
<thead>
<tr>
<th></th>
<th>Length of Stay in Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Cuddler Program</strong></td>
<td>26.2</td>
</tr>
<tr>
<td>Implementation of Cuddler Program</td>
<td>22.4</td>
</tr>
<tr>
<td>Continuation of Cuddler Program</td>
<td>23.9</td>
</tr>
<tr>
<td>Sustainability of Cuddler Program</td>
<td>20.95</td>
</tr>
<tr>
<td>Continued Sustainability of Cuddler Program</td>
<td>17.61</td>
</tr>
</tbody>
</table>
Supportive non-pharmacologic Rx
Infant Massage Therapy

- Infant-Parent attachment and bonding
- Stimulates production of oxytocin (pain relief and relaxation)
- Appropriate sensory stimulation
- Promotes better sleep
- Reduces hypertonicity
- Normalizes sleep-wake cycle
- Improves digestion

- Randomized Prospective Blinded Study
- Decrease LOS and post-natal drug exposure
- Improve short and long term neuro-developmental outcomes
Breast Feeding and NAS

- Encouraged in compliant women on a Methadone or Subutex program
- Contraindicated in heroin, cocaine and heavy alcohol use
- Marijuana and Alcohol exposure through breast milk results in delayed motor development at age 1
- Contraindicated in HIV positive mothers
- Not contraindicated in Hepatitis
Breast Feeding and NAS

- There is strong evidence that breastfeeding is beneficial in reducing the severity and intensity of symptoms of NAS.
- Many authors have suggested that the levels of methadone/subutex transmitted in human milk are below the threshold of physiological significance.
Breast Feeding and NAS

- Improved one-to-one time and interaction
- Positive effects of mother-child bonding
- Skin-Skin (Kangaroo) Care
- Other components of breast milk
- Helps establish the neonatal gut microbiome
- Improves digestion and decreases GI symptoms
Treatment of NAS
Pharmacologic

- Reserved for infants with more severe symptoms despite maximal supportive care.
- Individualized based on severity & specific drug exposure
- Adoption of strict protocol with management strategies based scientific information and best practices
- Treatment of non-opiate withdrawal with opium is contraindicated (use Phenobarbital, Ativan)
Biphasic withdrawal

- Exacerbation of withdrawal symptoms at one to two weeks of age after initial symptoms were under control.
- Methadone/Benzos   Subutex/Benzos
- Symptoms may not respond to a single drug regimen.
- Combination regimen (+Phenobarbital) associated with better response, faster weaning and earlier discharge.
When to treat
How to treat

- Consider treatment when three consecutive score are > 8 or the average of three consecutive scores is >8

- How fast to wean (by 10% for scores 5-8) (by 15-20% for score <5)
Treatment of NAS

- Morphine/Tincture of Opium
  - Drug of choice for opiate withdrawal
  - Morphine available as 4mg/ml
  - Tincture of Opium available as 10 mg/ml
  - Must be diluted by pharmacy to 0.4 mg/ml
  - Contains no additives or high alcohol content
  - Has a short half life
  - Improves sucking quickly
  - Superior treatment for diarrhea & GI symptoms
  - Decrease in incidence of seizures
  - **Contraindicated in non-opiate withdrawal**
  
  Side effects: Constipation, Sleepiness, Apnea
Treatment of NAS

- Paregoric
  - Contains Anhydrous morphine (0.4mg/cc)
  - Other ingredients with potential toxic side effects:
    - Camphor - a CNS stimulant
    - Ethanol - 45%
    - Anise oil - habituation
    - Benzoic acid – may cause acidosis, CNS depression, renal failure, hypotension, seizures
    - Glycerin - pulmonary edema
  - Longer duration of therapy
Treatment of NAS

Phenobarbital
- Preferred drug for non-opiate withdrawal
- Suppresses agitation well
- Add to opium when biphasic withdrawal pattern is noted
- Has not prevented seizures and has not decreased LOS
- May cause significant sedation and interfere with sucking and bonding
- High blood levels may cause apnea
- No effect on vomiting or diarrhea
- Associated with disruption of striatal synaptic development
- Induction of neuronal apoptosis in animal models
Treatment of NAS

- **Clonidine** α-2Adrenergic receptor agonist
  - Activates inhibitory neurons
  - Reduces noradrenergic activity reversing the cause of opioid withdrawal
  - Non narcotic causes significant reversal of symptoms after one dose
  - Did not improve poor sleeping
  - No serious adverse effects

- To be used together with an Opioid for NAS
**CLONIDINE Dose**

6 mcg/Kg/day : q 4 hrs

[1 mcg/Kg/dose q 4 hrs.] or [0.75mcg/kg/dose q3hrs.]

- The dose of Clonidine is started at the time infant meets criteria for pharmacotherapy (as soon as possible after the morphine) and maintained unchanged until the morphine has been weaned off. May wean morphine by 10-25% daily

- Order blood pressure q 4 hrs. for 48 hrs on starting (hypotension) and on stopping (rebound hypertension) Clonidine. Blood pressure are to be measure q day in between if they are stable for the first 48 hrs of starting Clonidine
Treatment of NAS

- Methadone
  - Alternative drug for narcotic withdrawal
  - PO and IV preparations
  - Used in a small number of infants
  - Long term studies not available
  
  - Long half life (24-48 hrs. after repeated doses)
  - Longer treatment
  - Initial dose: 0.1 mg/kg every 6 hrs.
Treatment of NAS

- Diazepam
  - Not successful as single agent in the treatment of NAS;
  - Sedation; Poor sucking; Increased late-onset seizures;
  - Slow metabolism and elimination

- Chlorpromazine
  - Used in the treatment of cocaine and amphetamine intoxication
  - Multiple side effects:
    * cerebellar dysfunction,
    * decreased seizure threshold,
    * hematologic problems
  - No role in NAS