In Utero Drug Exposure and Neonatal Syndrome

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Statement of Intent
- The policies, procedures, standards of care, electronic medical record documents, and orientation/staff development materials have been developed and implemented for use within Children’s patient care environment.
- It is the intent of Children’s to readily share these developed components as guidelines in the interest of assuring the highest quality of care for children. It is the responsibility of the user to assure the pertinence of information received as it applies to their own institution.

Objectives
- Discuss the scope of the problem of in utero drug exposure and neonatal abstinence syndrome
- Discuss the presentation, signs and symptoms of infants affected by neonatal abstinence syndrome
- Discuss some common treatments for NAS

Course Accreditation
- Children’s Hospitals and Clinics of Minnesota is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.
- Children’s of Minnesota designates this activity for 1.25 hours of continuing nursing education.
- To receive contact hours for today, the participant must:
  - View the video
  - Complete the post test and evaluation at the end of the session.

Disclosures
- The faculty and planners have disclosed that they do not have any commercial conflict of interest to report relative to this presentation. All other treatments to be discussed (including all NAS treatments), although widely used, are technically “off-label” uses for these medications.
- Accreditation does not imply that ANCC or Children’s endorse any commercial products displayed in conjunction with this educational activity.
Disclosure

• No conflict of interest to disclose

• The only FDA approved treatments for withdrawal in adults are:
  o Methadone for heroin and other opiates
  o Benzodiazepines for alcohol
    • These have been generalized by some physicians to pediatric populations, but safety and efficacy in patients less than 18 years of age have not been established.

• All other treatments to be discussed (including all NAS treatments), although widely used, are technically “off-label” uses for these medications.

Objectives

• Discuss the scope of the problem of in utero drug exposure and neonatal abstinence syndrome

• Discuss the presentation, signs and symptoms of infants affected by neonatal abstinence syndrome

• Discuss some common treatments for NAS

Overview

• Epidemiology
• Common Drugs of Abuse
• Detection/Testing
• Signs/Symptoms
• Scoring Systems
• Treatments
• Outcomes

Epidemiology of Drug Use in Pregnancy

• 1991 Seminars in Perinatology
  o Incidence of drug-exposed newborns ranges from 3% to 50% depending on the specific patient population.
    • Urban centers tend to report higher rates

• Narcotic use reported in 7.5% of pregnancies
  o Wilbourn et al. / Perinat Neonatal Nurs 2001;14:26-45

Epidemiology of Drug Use in Pregnancy

• Narcotic use in pregnancy is increasing in Canada.
Epidemiology of Drug Use in Pregnancy

- Substance Abuse and Mental Health Services Administration (SAMHSA)
  - Results of 2009 Survey on Drug Use and Health: National Findings
    - 4.5% of pregnant women age 15-44 years used illicit drugs in the past month.
    - 11.9% report alcohol use.

NSDUH (National Survey on Drug Use and Health) 2008/2009 estimates

**2 Year Averaged Rates**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Not Pregnant 15-44y</th>
<th>Pregnant 15-44y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit drugs</td>
<td>10.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Tobacco</td>
<td>27.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>54.4%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

Maternal Poly-Drug Use in A Rural Population

- Screened 2200 Well-Baby and NICU admission
  - Risk Criteria
    - Positive maternal drug history
    - Positive maternal drug screen
    - Current or previous CPS involvement
    - Other siblings not living with mother
    - Limited or no prenatal care
    - Positive history of STD
    - Unusual behavior noted by staff
    - Placenta abruption
    - Previous fetal demise
    - Previous preterm birth


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Opiate</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age [years]</td>
<td>26.7 ± 0.54</td>
<td>25.6 ± 0.7</td>
</tr>
<tr>
<td>Race, white [%]</td>
<td>90</td>
<td>60</td>
</tr>
</tbody>
</table>
| Maternal Poly-Drug Use in A Rural Population

- Rural drug-using women are
  - Mostly white, high-school educated, on Medicaid
  - NAS is less likely to be a problem in Urban centers since the drugs more commonly used in those settings are not associated with withdrawal
  - They will still have the same issues with home environments, foster care, etc.

Proper screening can allow earlier detection and may improve outcomes.

Eastern Kentucky

“Oxycotin Express” or “Kentucky Pain Pill Pipeline”

- Author is the Medical Director for diagnostic center.
- Noticed requests from pain clinics in central Florida for authentication of MRI results.
- 61% of requests made from 2004 to 2009 were forged documents.
- Many of the pain clinics operate on a cash basis and have their own pharmacy.
- The diagnostic center instituted a policy that the pain clinics would have to obtain aKASPER report on the patient to verify no drug abuse. Some refused.
- Kentucky All Schedule Prescription Electronic Reporting

Eastern Kentucky

- True story from February 2011
- Vehicle stopped in central Kentucky.
  - Driver charged with:
    - Reckless Driving
    - Driving Under the Influence—second offense
    - Driving on a suspended license
    - Possession of narcotics with intent to distribute
    - Possession of drug paraphernalia
    - Possession of a concealed deadly weapon without a permit
    - Dead body in the back seat
- Trio had been to central Florida. Deceased woman suffered an overdose of narcotics. Driver thought she was “sleeping it off”.

Why Drug Abuse?
General Mechanism of Reward

- Activation of specific neural pathways that originate in the pons and midbrain and project to the forebrain.

  - Amygdala
  - Ventral Medial Prefrontal Cortex
  - Anterior Cingulate Cortex
  - Ventral Pallidum
  - Nucleus Accumbens

The action of most drugs of abuse is to modulate dopamine levels in the nucleus accumbens.
- Causes feelings of euphoria
- Chronic opiate use induces neuroadaptations.

Opioids
- Agonists
- Antagonists
- Mixed agonist-antagonists
- Semi-synthetic opioids

CNS stimulants
- Amphetamines
- Methamphetamines
- Cocaine
- Methylphenidate (Ritalin)
- Pemoline (Cylert)
- Phenylpropanolamine
- Phencyclidines

Mechanism of Cocaine
Specific Drugs of Abuse

- **CNS depressants**
  - Alcohol
  - Barbiturates
  - Benzodiazepines
  - Cannabinoids (marijuana, hashish)

- **Other sedative-hypnotics**
  - Methaqualone (Qualaude)
  - Ethchlorvynol (Placidyl)
  - Glutethimide (Doriden)
  - Methyprylon (Noludar)
  - Ethinamate (Valmid)
  - Chloral hydrate

Specific Drugs of Abuse

- **Hallucinogens**
  - LSD
  - Phenylethylamine (mescaline)
  - Phenylisopropylamines (MDA, MMDA, MDEA, MDMA [3,4-methylenedioxymethamphetamine or ecstasy])

- **Inhalants**
  - Solvents and aerosols (glues, gasoline, paint thinner, etc.)

- **Nitrites**

- **Nitrous oxide**

SSRIs

- **WHO Database Review**
  - 64 with paroxetine
  - No discussion of treatment

  - Regardless of if you call it “withdrawal” or not, SSRIs do have an effect on the fetus/newborn.

- **Late gestation in utero exposure to SSRIs is associated with a neonatal behavioral syndrome characterized particularly by CNS symptoms.**
  - Symptoms seem to resolve over the course of days with supportive treatment in most cases.
  - If pharmacotherapy is needed, the best approach is unclear.

  Moses-Kolko. JAMA May 2005;293(19):2372-2383

Medication Assisted Treatment of Addiction in Pregnancy
Addiction Treatment During Pregnancy

- Abstinence is not likely to be effective and may be a barrier to seeking treatment.

- Medical treatment usually consists of replacement and maintenance on a controlled and supervised regimen.

- May have to increase dose in last few weeks of pregnancy due to increased maternal metabolism and volume of distribution.

Addiction Treatment During Pregnancy

- **Methadone**
  - Used for decades
  - Most commonly prescribed opioid in pregnancy since 1965.
  - Causes NAS in 60-80% of pregnancies
  - Length of treatment about 3 weeks

- **Morphine**
  - Oral, slow-release
  - Length of treatment about 2 weeks

- **Buprenorphine**
  - Multiple small studies suggest less NAS and shorter length of treatment (1.1 days)
  - Actual experience may vary. New data expected soon.


Description

- Babies were exposed to the following drugs:

<table>
<thead>
<tr>
<th>Description</th>
<th>CONT</th>
<th>BUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Methadone</td>
<td>159</td>
<td>24</td>
</tr>
<tr>
<td>Prescription Pain Meds</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Cocaine</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>THC</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Phenergan</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>2</td>
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Results

<table>
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<tr>
<th></th>
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<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>155</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>GA at Birth (mean, wks)</td>
<td>38</td>
<td>39</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length of hospitalization (median, days)</td>
<td>10</td>
<td>17</td>
<td>0.002</td>
</tr>
<tr>
<td>Length of inpatient treatment (median, days)</td>
<td>4</td>
<td>15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Outpatient Length of Treatment (median, days)</td>
<td>0</td>
<td>8.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Total Length of Treatment (median, days)</td>
<td>4</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multi-Drug Therapy</td>
<td>17 (11%)</td>
<td>6 (25%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Required outpatient treatment</td>
<td>40 (26%)</td>
<td>14 (58%)</td>
<td>0.003</td>
</tr>
<tr>
<td>No pharmacologic treatment required</td>
<td>62 (40%)</td>
<td>4 (17%)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Detection
Detecting Drug Exposure

Maternal Screening
- History, Self Report
  - Unreliable, depends on patient and interviewer
  - Canadian Study
    - Neonatal urine testing indicates 27% of mothers did not admit to substances detected in the infant.
    - 24% of meconium screens detected additional substances other than what the mothers admitted to.

- Suspicion (Risk Factors)
  - Gravida 4 or more
  - No or late prenatal care
  - Previous children not living with mother
  - History of CPS involvement
  - Abruption
  - Physical injuries
  - History of chronic pain
  - STDs, Other risky behavior
  - Disorientation, confusion during interviews

  - Maternal urine or hair testing

Maternal Dosage and NAS
- It is commonly accepted that the maternal dose of the replacement therapy does not affect the risk of NAS.
  - Studies are confounded by poly-drug exposure
    - Mixed results
    - It is thought by some that larger doses late in pregnancy do correlate with the risk of symptoms.
    - Weaning dose late in pregnancy vs. maintaining or escalating
    - Symptoms do correlate with cord-blood methadone levels
    - Differences in pharmacogenetics/kinetics can lead to variation in cord-blood levels.

- No Narcan (naloxone) to an infant of a known opiate-using (heroin) mother.
  - Abrupt withdrawal can illicit seizures
  - Has been removed from NRP as a resuscitation medication.

Detecting Drug Exposure

Infant Screening
- Urine Drug Screen
  - Detects recent exposure
- Meconium Drug Screen
  - Detects prolonged or not recent exposure
  - Beyond 20 weeks gestation
  - Expanded opiate testing required to detect oxycodone, propoxyphene and methadone
  - May not be available
    - Early passage (fetal stress), limited or delayed passage (very preterm)
- Universal Screening?
  - Regulations, privacy?

Other tests
- Umbilical cord tissue
  - Easy, noninvasive, quick, long window of exposure detection
  - Specialized testing
- Neonatal hair
  - Present on the fetus after 6 months of gestation
  - Can be used during the first 3 months of life
Signs/Symptoms

General Mechanism of Withdrawal
- Increased firing rate of the locus coeruleus and elevated activity of in the autonomic nervous system.

Signs/Symptoms
- CNS dysfunction
  - High-pitched cry
  - Restlessness
  - Hyperactive reflexes
  - Jitteriness
  - Tremors
  - Hypertonia
  - Myoclonic Jerks
  - Seizure

- Metabolic and Vasomotor Disturbance
  - Sweating
  - Fever
  - Mottling
  - Yawning

- GI Dysfunction
  - Excessive Sucking
  - Poor Feeding
  - Hyperphagia
  - Vomiting
  - Loose Stools
  - Severe diaper rash

- Respiratory Symptoms
  - Sneezing
  - Nasal Flaring
  - Tachypnea
  - Apnea

- Other
  - Abrasions
  - Excoriations

Videos are not available
Drug Effects vs. NAS

- Early exposure affects brain growth and development
  - Decreased head circumference and other growth parameters
  - μ-receptor agonist exposure results in decreased cortical neuronal density, smaller dendritic arborization and branching in animal studies.
    - μ agonists decrease cell division
  - Can result in hypertonicity, hypereflexia, irritability, tremors, shrill cry and behavioral disturbances.
- Gross structural abnormalities have been reported
  - Hydrocephalus and heroin
  - Stroke and codeine

Neonatal Abstinence Syndrome and Cerebral Infarction Following Maternal Codeine Use During Pregnancy

REYNOLDS EW, RIEL-ROMERO RMS, BADA HS
CLIN PEDIATR 2007;46(7):639-645

Codeine-Containing Cough Medication

- Codeine is an opiate and can cause NAS.
- Many women do not consider prescription cough syrups when asked about drug use.
- Opiate use in pregnancy has been linked to perinatal cerebral infarction.

Case 1

- 39-week infant, unremarkable delivery
- Mother denies any history of drug use.
- 2 weeks prior to delivery, the mother had a severe URI for which she was prescribed a combination cough preparation.
  - 6.25mg promethazine HCl / 5 ml
  - 10 mg codeine phosphate / 5 ml
  - Total dose 500-600 mg of codeine

Case 1

- At a few hours of life the baby had abnormal posturing with arching and seizures.
- Baby drug screen positive for codeine and morphine.
  - (Codeine is metabolized to morphine.)
- Evaluation
  - EEG
    - Subclinical seizures arising from the left hemisphere
  - All other work-ups including sepsis, coagulopathy, cardiology and metabolic disease profiling were negative.
- Imaging
  - MRI on DOL 3
    - Left middle and anterior cerebral artery infarction
    - Edema of the left cerebral peduncle and pons
    - Residual clot in the internal carotid artery
Case 1
- NAS symptoms were controlled with phenobarbital, and the baby was discharged to home.
- 2 month follow-up:
  - No seizures but persistent focal neurologic findings

Case 2
- 38-week infant, unremarkable delivery
- No maternal drug history
- 2 weeks prior to delivery the mother was hospitalized with pneumonia
  - Treated with a codeine containing-cough medicine
- 33 hours of life, baby developed clinical seizures
  - Seizures controlled with combination of phenobarbital and lorazepam

Case 2
- EEG
  - Ictal discharges from the left hemisphere with associated clinical desaturation episode
  - Bihemispheric slow wave activity (diffuse cerebral dysfunction)
  - All other work-ups including sepsis, coagulopathy, cardiology and metabolic disease profiling were negative.

Case 2
- MRI
  - Infarction in the left occipito-temporal region
  - Old blood and hemosiderin deposition
  - Occipital encephalomalacia
Case 2
- NAS symptoms were controlled with medication.
- Follow-up
  - Infant was discharged to home with phenobarbital and lorazepam treatment.
  - Good seizure control at 1 year follow-up

Discussion
- Diffuse cerebral infarction has been described as a result of other drugs that induce vasospasm and hypercoaguability.
  - Methanol
  - Cocaine
  - Heroin

Discussion
- Codeine, like other opiates, can have adverse effects on the fetus and neonate.
- This class of drugs is known to have effects on cerebral vasculature.
- Importance of history taking cannot be over emphasized.
  - Ask the right question!
  - Mother may not consider prescribed cough medicine when asked about drug use.
- NAS can occur in infants of “non-addicted” mothers.

Discussion
- Routine, universal urine or meconium drug screens may be warranted.
- Physicians should consider maternal opiates or codeine use when evaluating a newborn with perinatal stroke.
- These findings could easily be generalized to other drugs or medications with vaso-occlusive properties or drugs which induce hypercoaguabale states.

Symptom Assessment

Scoring Systems
- All are based on opiate withdrawal
  - May not be effective for all types of exposure
- Most are based on behaviors of term newborns
  - May not be appropriate for preterm infants
  - Older infants may require adjustments to the interpretation of the scores.
- Decision to initiate treatment based on single or serial scores
  - No studies compared different thresholds for starting treatment as to short-term outcomes.
Finnegan Scoring

- Finnegan
  - Assessment of 21 common symptoms of NAS with weighted scores for each symptom
    - Pharmacotherapy after score of 8
    - Most commonly used form
  - Considered too complex by some

Finnegan Scoring

<table>
<thead>
<tr>
<th>System: CNS Disturbances</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry (excessive, continuous)</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Sleep (&lt;1, 2, 3 hrs after feed)</td>
<td>3 - 2 - 1</td>
</tr>
<tr>
<td>Reflexes</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Tremors</td>
<td>1 - 2 – 3 - 4</td>
</tr>
<tr>
<td>Increased Muscle tone</td>
<td>2</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>3</td>
</tr>
<tr>
<td>Convulsions</td>
<td>5</td>
</tr>
<tr>
<td>Excoriations</td>
<td>1</td>
</tr>
</tbody>
</table>

Finnegan Scoring

Gastrointestinal Disturbances

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive Sucking</td>
<td>1</td>
</tr>
<tr>
<td>Poor Feeding</td>
<td>2</td>
</tr>
<tr>
<td>Regurgitation / projectile vomiting</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Loose stools / watery stools</td>
<td>2 - 3</td>
</tr>
</tbody>
</table>

Respiratory System manifestations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Flaring</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory rate &gt;60/min / RR &gt;60/min and retractions</td>
<td>1 - 2</td>
</tr>
</tbody>
</table>

Finnegan Scoring

Other Disturbances (Autonomic)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Fever 37.3 – 38.3°C / =&gt;38.4°C</td>
<td>1 - 2</td>
</tr>
<tr>
<td>Frequent yawning (&gt;3-4 in 4 hr)</td>
<td>1</td>
</tr>
<tr>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>2</td>
</tr>
<tr>
<td>Sneezing (&gt;3-4 in 4 hr)</td>
<td>1</td>
</tr>
</tbody>
</table>

Lipsitz

- 11 items...less focus on autonomic dysfunction
  - Does not include sleep, myoclonic jerks, seizure, suckle feeding, retractions, flaring (includes rate and sneezing) or sweating.
  - Only provides subjective ratings of some symptoms (yes/no)
  - Pharmacotherapy after score of 4

Ostrea

- 6 item simple scale (yes/no)
  - no guidelines for pharmacotherapy
  - Does not allow for summing of multiple symptoms,
  - Widely viewed as insufficient

Scoring Systems

Neonatal Withdrawal Inventory

- Checklist of 7 NAS symptoms, 4 point behavioral distress scale
  - Pharmacotherapy after score of 8

Neonatal Narcotic Withdrawal Index

- 6 signs of NAS plus “other” category of 12 signs
  - Pharmacotherapy after score of 5

Neonatal Brazelton Neurobehavioral Scales (NBAS)

- 5 symptoms, No guidelines for pharmacotherapy, Requires certified examiner

Neonatal Network Neurobehavioral Scales (NNNS)

- Similar to NBAS, Includes stress/abstinence signs
  - May be helpful in preterm infants
Treatments

Treatment: Nonpharmacologic

- Supportive Treatment
  - Swaddling, Positioning
  - Small frequent feedings with high calorie formula
    - Lactose-free formula?
  - IV fluids
  - Decrease sensory stimulation
  - Monitor closely for other diseases
  - Monitor weight gain (too much or too little)
  - Bundle assessments, interventions and examinations
  - Environmental control

Swaddling

C-Position

C-Position Facing Out
Place your infant in C-hold with chin down, legs up, arms forward with back rounded forward. Place the baby away from your body. This hold is good for infants with increased tone using your body to break the baby's tendency to arch backward by molding his or her body forward.

Side-Lying with Boundaries

Vertical Rock

Clap and Sway

Treatment: Pharmacologic

- Goals
  - Treat with drug from same class as exposure
  - Minimize symptoms
  - Promote appropriate growth and weight gain
  - Promote caretaker-child interaction

- Concerns about multiple exposures and “therapeutic” sedation effects.
  - Optimal regimen has not been established.
    - Considerable heterogeneity in the diagnosis and treatment.

- Only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs.
  - Unknown if long-term morbidity is changed by pharmacotherapy.

- Morphine
  - Often requires frequent dosing, most common treatment.
  - Wide range in reported length of treatment (8-79 days)*

- Methadone
  - Long half-life allows q day dosing but makes titration difficult

- Phenobarbital
  - Q day dosing, monitoring levels encouraged
  - Commonly used as a second-line or adjunctive therapy

- Tincture of Opium
  - Measured in drops/kg. Frequent dosing.
  - TOO + Phenobarbital is more effective than Phenobarbital alone

- Paregoric
  - Declining use due to side effects
    - Contains isoquinolone, camphor, ethanol, anise oil, benzoic acid, benzyl alcohol, glycerine
    - Very good for control of GI symptoms

- Chlorpromazine
  - Controls GI and CNS symptoms
  - Slow elimination (1/2 life = 3 days)
  - Contains benzyl alcohol
  - Side effects include cerebellar dysfunction and decreased seizure threshold

- Diazepam
  - Concerns for poor feeding, increased sedation, seizures
  - Contains benzyl alcohol and sodium benzoate
    - Contraindicated in jaundiced and preterm infants
      - Bilirubin displacement

- Buprenorphine
  - Few studies. Mostly small safety studies
  - Suggestion of shorter treatment

*Traft et al. Addiction. 2010;106:574-580
Treatment: Pharmacologic

- Clonidine
  - Nonnarcotic, stimulates postsynaptic alpha-adrenergic receptors in the depressor site of the vasomotor center of the medulla (decreases sympathetic outflow)
  - Effective for treatment of abstinence syndrome in adults
  - 1984 NAS study (n=7)
    - Symptoms controlled in 6 infants
    - Shorter length of treatment (retrospective controls)
  - 2009 NAS study (n=14, 3 from maternal opiate) IL
    - Lower NAS scores after starting treatment with clonidine
  - 2010 NAS study (n=133) Germany
    - 29 Clonidine +/- Chloral Hydrate, 64 Morphine +/- Phenobarbital
    - Shorter LOS in clonidine group (14 vs. 35 days)

National Survey: Management of NAS

- 75 / 102 responded
- 41 (55%) have a written policy on management
- 49 (65%) use Finnegan Scores

Treatments

- Opioid exposure: 63% use tincture of opium or morphine
- Polydrug exposure: 52% use tincture of opium or morphine

National Survey: Management of NAS

First Line | Added Second Line
--- | ---
Opioids - 47(63%) | Phenobarbital (24), IV morphine (10), Methadone (8), Clonidine (3), Diazepam (2)
Methadone - 15(20%) | Oral morphine (6) Phenobarbital (4), Tincture Opium (3), Clonidine (2)
Phenobarbital – 13(17%) | Oral morphine (4), Methadone (4), Tincture of opium (3), Diazepam (2)

First Line | Added Second Line
--- | ---
Opioids – 39 (52%) | Phenobarbital (27), Methadone (3), Clonidine (2), Diazepam (1), Variable (6)
Phenobarbital – 24(32%) | Opioids (8) Diazepam (8), Methadone (4), Rarely seen (4)
Methadone – 8 (10.6%) | Phenobarbital (4), Opioids (3), Diazepam (1)
Rarely seen – 4 (5.4%) | Phenobarbital (4), Opioids (3), Diazepam (1)

Opioid Exposure

- Common Treatment
  - Morphine 0.1 mg per dose q 4 hours, titrate to effect for scores over 8 (or 10).

- UCSF website
  - DTO 0.1 mL/kg q 3-4, increase by 0.05-0.1 mL increments until symptoms controlled.
  - Can use phenobarbital or diazepam as adjunctive treatments

Polydrug Exposure

- Newborn Emergency Transport Services (NETS) (Australia)

<table>
<thead>
<tr>
<th>Score</th>
<th>Dosage (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 consecutive scores</td>
<td></td>
</tr>
<tr>
<td>average 8 or more</td>
<td>0.5 mg/kg/day</td>
</tr>
<tr>
<td>divided q 6 hours</td>
<td></td>
</tr>
<tr>
<td>2 consecutive scores</td>
<td></td>
</tr>
<tr>
<td>average 12 or more</td>
<td>0.5-0.7 mg/kg/day</td>
</tr>
<tr>
<td>divided q 6 hours</td>
<td></td>
</tr>
</tbody>
</table>

- Treat with morphine as noted.
- Use birth weight for calculations
- Change to q 4 dosing if symptoms are not controlled on q 6.
Treatment Regimens

**Another US academic center**

For 3 consecutive scores ≥8... or 2 consecutive scores ≥12...
or 1 score ≥15: Begin morphine 0.05 mg/kg/dose q 4 p.o.
For 2 scores ≥15 use IV morphine at 0.1 mg/kg/dose q 4
Change to oral dosing when scores are less <12
Increase dose by 0.05 mg/kg/dose for 3 scores over 8 or 2 scores
over 12. Max dose 0.8 mg per dose.
Add phenobarbital if morphine is at 0.1 mg/kg and increased doses
are required.
Wean morphine 10% when no more than 2 scores >8 in a 24 hour
period. Wean dose every 48%.

When dose is 0.025 mg/kg/dose, increase interval sequentially to 6,
8 and 12 hours. If phenobarbital was started, d/c 24 hours post
morphine.

Finnegan Scoring Q 3 hour.

- If baby receives a score other than Cat 0, rescore in 1 hour.
- If baby returns to Cat 0, return to q 3 hour scoring.
- If baby continues to score in a category other than 0, use the
  higher score to determine the treatment dose.

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Initiation of Oral Morphine Treatment</th>
<th>Dose Escalation</th>
<th>Dose Re-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 0</td>
<td>0-8</td>
<td>Return to q 3 scoring</td>
<td>no change</td>
<td>not applicable</td>
</tr>
<tr>
<td>Category 1</td>
<td>9-12</td>
<td>0.04 mg q 4 hours</td>
<td>0.02 mg per dose</td>
<td>0.01 mg per dose</td>
</tr>
<tr>
<td>Category 2</td>
<td>13-16</td>
<td>0.08 mg q 4 hours</td>
<td>0.04 mg per dose</td>
<td>0.02 mg per dose</td>
</tr>
<tr>
<td>Category 3</td>
<td>17-20</td>
<td>0.12 mg q 4 hours</td>
<td>0.06 mg per dose</td>
<td>0.03 mg per dose</td>
</tr>
<tr>
<td>Category 4</td>
<td>&gt;20</td>
<td>0.16 mg q 4 hours</td>
<td>0.08 mg per dose</td>
<td>0.04 mg per dose</td>
</tr>
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When Category 0 scores are obtained for 48 hours on a
particular morphine dose, begin weaning.
- Wean dose by 0.02 mg q 24 hours as long as scores remain in
  Category 0.
- If a score other than Category 0 is obtained during the
  weaning process, rescore in 1 hour to determine if an
  increased dose is required. Re-escalate the dose
  according to the chart.

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Pediatric Interim Care Center (Neonatal abstinence hospital in
Kent, WA).

- Use Finnegan Score System
- Treat if NAS score >10 x 3 or >12 x 2 in a 24 hour period.
- Wean dose every 48%.

- Morphine 0.4 mg/mL
  0.2 mL po q 3 hours (coincides with feeding)
  Increase dose by 10% every 3 hours until symptoms are controlled.
  Increase by 10% during later course of treatment if NAS scores
  increase.
  Monitor for side effects...HR<80 or RR <25.
  Wean dose by 5% once a day when scores are regularly <5 and no
  scores >10 until dose is 0.16 mL

Analysis of Treatments

- Cochrane meta-analysis
  7 studies—585 infants—1983-2004
  1 study of oral morphine vs. non-pharmacologic treatment
    Morphine increased duration of treatment and length of
    hospitalization, but reduced days to regain birthweight
- 4 studies compared opioids to phenobarbital
  4 No difference in treatment failures
  1 study reported less seizure in opioid treated infants than
  those with supportive care only.
  3 studies showed less treatment failure with opioids than with
diazepam.


2nd Cochrane review

- 6 trials—305 infants—1969-2002
  Sedative treatment vs. nonopioid treatment
  Phenobarbital increased length of treatment and hospitalization
  Study of second line treatment after failure on DTO
  Phenobarbital shortened hospital stay and decreased opioid dose.
  Phenobarbital vs. diazepam—less failure in phenobarb group
  Phenobarb vs. Chlorpromazine—no difference

Other Studies

- Oral morphine vs. DTO
  - No difference for duration of treatment, duration of hospitalization or weight gain.

- Methadone vs. Morphine
  - No difference in length of hospitalization

- Morphine vs. Phenobarbital
  - Shorter treatment with phenobarbital

- Buprenorphine vs. DTO
  - Non-significant reduction in LOS with Bup

To Breastfeed or Not To Breastfeed, That is the question?

- Controversial
  - Continued exposure to maternal drugs of abuse
    - Little transmission to breastmilk
    - Helps control the symptoms of NAS
    - What if mother is in a program with close monitoring?
  - CAUTION
    - Contraindicated if continued use of THC

Codeine in Breast Milk

- 2006 report of a Toronto infant
  - Mother given Tylenol 3 for episiotomy pain.
    - Initially 2 tab (60mg) q 12, but cut to 1 tab (30mg) q 12 after 2 days
      - Less than the usual amount required
    - At 7 days of life, parents noticed the infant to be lethargic.
    - At 11 days of life, baby was brought to the pediatrician for poor feeding and jaundice.
    - On day 13 he was dead.

- Swallow-Breath Interaction and Drug-Exposure
  - During nonnutritive suck in low-risk preterm infants, swallow and breath interact in 2 ways.
    - How: Central Apnea, Obstructive Apnea, Attenuated Respiration. (Sw:Br)
    - Where: Babies can swallow at any point in the respiratory cycle: Beg Exp, Mid Exp, End Exp, Mid Insp, Apnea. (POR)

Codeine in Breast Milk

- Codeine is metabolized to morphine by O-demethylation by CYP 2D6 (part of P450 system).
  - Mother carried three copies of CYP 2D6 gene
    - She is an “ultra-rapid” metabolizer of codeine to morphine
  - Maternal grandfather, FOB and baby had 2 copies
    - They are “rapid” metabolizers.
  - “Ultra-rapid” metabolizers by ethnicity
    - Finland/Denmark 1% Ethiopia 29%
    - Greece/Portugal 10% African and Asian 30%
  - Limit codeine use in pregnant and breast-feeding mothers.

Codeine in Breast Milk

- Autopsy found the infant to have a blood morphine level of 70 ng/ml.
  - 6x higher than normally considered safe for neonates
- The mother’s breast milk had a morphine concentration of 87 ng/mL.
  - Typical range of milk concentrations after 60 mg every 6 h is 1.9–20.5 ng/mL.
Swallow-Breath Interaction and Drug-Exposure

- During nonnutritive suck in low-risk preterm infants, swallow and breath interact in 2 ways.
  - How: Central Apnea, Obstructive Apnea, Attenuated Respiration. (Sw:Br)
  - Where: Babies can swallow at any point in the respiratory cycle: Beg Exp, Mid Exp, End Exp, Mid Insp, Apnea. (POR)
  - The “How” is affected by the amount of practice the infant gets...Learning?
  - The “Where” is not affected by practice...Maturation?

Swallow-Breath Interaction and Drug-Exposure

- We compared a drug-exposed cohort to a group of term control infants.
  - The NAS infants differ from the term controls in the type of Sw:Br interaction, but not in the POR.
  - The maturational component progresses similarly in the control and NAS infants.
  - The learned component does not progress the same at the control infants.
    - Do they ever catch up?
    - Do they have to catch up?
    - Long term questions?
    - Implications?
Baby Outcomes

Outcomes

- Few studies
- Confounding variables:
  - unsafe/unhealthy home environment,
  - dysfunctional care-givers,
  - fetal growth restriction,
  - poly-drug exposure
- Barker Hypothesis: alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, predisposing individuals to later disease

Bayley scores do not seem to be affected by choice of treatment (phenobarbital, paragoric, both)
- Small study (n=69)
- Withdrawal associated seizures do not carry increased risk of poor outcome.

Kaltenbach K, Finnegan L.P. Neurotoxicology Teratol 1986;8:353-355

Nursing Outcomes

- NICU nurses spend a large amount of time soothing the affected infant, educating and consoling the family.
- Parents may fear exposure as a “bad” person or risk losing the child to welfare system. May detach or distance themselves from the infant.
- Nurse becomes the only care-provider for the unattended infant.
- 2010 Canadian survey of NICU nurses caring for babies affected by NAS
  - 24 nurses employed by the NICU in the study, 14 completed the survey
  - All female, 20-55 years old, 6m to >20y experience

Nursing Experience

- 2 themes present in all questions
  - Commitment to the infant
    - Surprise?
    - Provides context for understanding the conflicts inherent in caring for infants with NAS
  - Conflict between skilled nursing role and surrogate mother
    - NICU nurses have advanced training and specialized skill sets
    - Resuscitation, caring for infants with terminal illness
    - Perception that NAS babies are less sick but very demanding
Nursing Experience

- 3 themes for specific questions
  - Disconnect between expectations of nurses and families
    - Empathy for the baby is easy...empathy for the mother is difficult
  - Stress, Frustration, Burnout
    - Physically and emotionally draining
    - Demand extensive amounts of time that can’t be spent with other infants
  - Increased awareness of drugs at home and community
    - Increased discussion with own children about risks

- NICU nurses are committed to caring for infants despite adversities.
- Key issue to be addressed is the attitude of nurses towards addicted mothers
- Organizations can support nurses with specialized training in understanding addiction and creative scheduling to distribute difficult babies, lessen frustration with infant and family and improve nurse-family interactions.

Summary

- NAS is common in the NICU
  - Proper screening and surveillance can provide earlier treatment and potentially better outcomes.
  - Drugs of abuse vary by location and population.
    - Urban centers often see cocaine and heroin
    - Rural populations seem to be using more prescription drugs (oxytocin, methadone)
  - Symptoms are observed and scored with various systems.
    - Finnegan Score is the most widely used
    - Each has intrinsic limitations
  - There are many treatment options available.
    - Few have been studied adequately.
    - "Best" treatment is unclear.
    - Don’t forget about care-givers when designing plans to care for these infants.

- Clinical Report from the AAP Committee on Drugs and The Committee on the Fetus and Newborn

Question

- What about babies of methamphetamine users?

- Is there an association between methamphetamine use and gastroesophageal reflux cases?
Question
How soon after delivery do the withdrawal symptoms begin?

Question
Do infants who are exposed to drugs in utero show a greater tendency to become addicted to drugs later in life?