WHAT WORKS IN NAS TREATMENT

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I have no conflicts of interest (financial or otherwise) that are germane to this presentation.

Our center will be participating in a multi-center NIH-funded study comparing the efficacy of methadone and oral morphine in the treatment of NAS.
EFFECTS OF OPIOIDS ON FETUS/CHILD

Slight increase in risk of congenital heart disease, neural tube defects, and gastroschisis (odds ratios 1.8-2.7:1)

Decreased fetal growth

Neurobehavioral abnormalities at birth (NAS)

Long term effects – small and variable increase in:
- Behavioral problems
- Attention deficit disorder
- Memory/perception issues

Unknown effects on IQ and executive functioning
TOPICS OF INTEREST: PREVENTION

Primary prevention:

- Contraception
- Education of providers and the public
- Role for inpatient medically supervised maternal detoxification?
- Effect of maternal drug(s) on likelihood, timing, and severity of NAS

Secondary prevention:

- Prenatal identification of at risk infants
- Monitoring of at risk infants
# MATERNAL OPIOIDS

<table>
<thead>
<tr>
<th>OPIOID:</th>
<th>HEROIN</th>
<th>METHADONE</th>
<th>BUPRENORPHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>Short (2-6 hours)</td>
<td>Long (24 hours)</td>
<td>Long (24+ hours)</td>
</tr>
<tr>
<td>Onset of signs</td>
<td>Usually &lt; 24 hours</td>
<td>Usually 24-48 hours but may be 3-7 days</td>
<td>Usually 24-72 hours</td>
</tr>
<tr>
<td>Severity of signs</td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Likelihood of NAS</td>
<td>Lowest (50-70%)</td>
<td>Highest (up to 94%)</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>
**METHADONE VS. BUPRENOORPHINE**

**Mothers’ Buprenorphine Treatment During Pregnancy Benefits Infants**

- **Hospital Stay**
  - Methadone (n=73): 18 days
  - Buprenorphine (n=58): 10 days

- **Duration of Withdrawal (Neonatal Abstinence Syndrome) Treatment**
  - Methadone (n=73): 10 days
  - Buprenorphine (n=58): 5 days

- **Total Dose of Morphine**
  - Methadone (n=73): 15 mg
  - Buprenorphine (n=58): 5 mg

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VARIABILITY OF NAS

Maternal factors: Drug, amount, frequency, cofactors (e.g., benzos, EtOH, cocaine, marijuana), stress, other co-morbidities

Placental factors

Infant factors: Gestational age, co-morbidities, environmental and caregiver differences, efficacy of treatment

Genetic and epigenetic factors
TOPICS OF INTEREST: PREVENTION

Primary prevention:
  Contraception
  Role for inpatient medically supervised maternal detoxification?
  Effect of maternal drug(s) on likelihood, timing, and severity of NAS

Secondary prevention:
  Prenatal identification of at risk infants
  Monitoring of at risk infants
TOPICS OF INTEREST: TREATMENT

Treatment issues:
  - Quantification of severity of NAS
  - Goals of treatment
  - Non-pharmacologic approach
  - Role of breast feeding
  - When to use pharmacologic treatment
    - What drug(s); what dosage regiments; how to wean
  - Role of outpatient management; post-discharge follow-up
## Finnegan Score

<table>
<thead>
<tr>
<th>SYSTEMS</th>
<th>SIGNS AND SYMPTOMS</th>
<th>SCORE</th>
<th>AM</th>
<th>PM</th>
<th>DAILY WT.</th>
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</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>High Pitched Cry</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Continuous High Pitched Cry</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Sleeps &lt; 1 Hour After Feeding</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 2 Hours After Feeding</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Hyperactive Moro Reflex</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Markedly Hyperactive Moro Reflex</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Disturbed</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Disturbed</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Undisturbed</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Undisturbed</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Increased Muscle Tone</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<td></td>
<td>Excoriation (specify area:)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Myoclonic Jerks</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<td></td>
<td>Generalized Convulsions</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Metabolic/Vasomotor/Respiratory</td>
<td>Sweating</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Disturbances</td>
<td>Fever &lt; 101°F (39.3°C)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Fever &gt; 101°F (39.3°C)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Frequent Yawning (&gt; 3-4 times/interval)</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Mottling</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Nasal Stiffness</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Sneezing (&gt; 3-4 times/interval)</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Nasal Flaring</td>
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<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Respiratory Rate &gt; 60/min</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Respiration Rate &gt; 60/min with Retractions</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Gastrointestinal Disturbances</td>
<td>Excessive Sucking</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td></td>
<td>Poor Feeding</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Regurgitation</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Projectile Vomiting</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
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<tr>
<td></td>
<td>Loose Stools</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Watery Stools</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
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</tbody>
</table>

### TOTAL SCORE

**SCORER'S INITIALS**

**STATUS OF THERAPY**

GOALS OF TREATMENT

Minimize signs of NAS
Ensure normal growth (rate of weight gain)
Establish normal sleep-wake cycles
Promote normal socialization (caretaker-child interactions)
Avoid known complications; e.g.,
  • Fever
  • Skin breakdown
  • Seizures
NON-PHARMACOLOGIC TREATMENT

Swaddling
C-Position
Vertical rock
Head to toe movement
Percussion
Small frequent high caloric feedings; nursing when indicated
Minimize external environmental stimuli
Introduce stimuli gradually
Intravenous hydration as necessary
CONCURRENT TREATMENT OF FAMILIES

Recognize that mother always feels anxiety and guilt
Show empathy
Project a non-judgmental attitude
Evaluate maternal (and familial) psychosocial status
Work toward establishing good parental-infant bonding, teach parenting skills, with goals to:
  • Avoid later child abuse and neglect
  • Promote long-term supportive environment
Educate family about resources
PHARMACOLOGIC TREATMENT

Goal of pharmacologic treatment is to allow infant to tolerate mild signs of withdrawal (feed, sleep, interact)

Medications that have been used to treat NAS include:

• Morphine, methadone, buprenorphine (opioids)
• Phenobarbital (barbiturate)
• Diazepam, lorazepam, clonazepam (benzodiazepines)
• Clonidine ($\alpha_2$-adrenergic agonist)
• Chlorpromazine (phenothiazine)
FIRST LINE DRUG TREATMENT (U.S. AND U.K.): OPIOID (ORAL MORPHINE > METHADONE), BUT SIGNIFICANT USE OF PHENOBARBITAL

INITIAL DOSE IS USUALLY TITRATED TO FINNEGAN SCORES

IF SIGNS OF NAS ARE NOT RELIEVED BY MAXIMUM DOSE OF SINGLE DRUG, A SECOND DRUG IS ADDED (PHENOBARBITAL > CLONIDINE > BENZODIAZEPINE)

DOSE IS WEANED BY 10-20% EVERY 1-2 DAYS SO LONG AS FINNEGAN SCORES ARE GENERALLY < 8
CURRENT STATE OF EVIDENCE

Existing trials do not clearly identify the most effective pharmacologic drug class or the most effective agent within a drug class (endpoints: treatment failure; length of stay; total dose of drug) and have methodological weaknesses.

Protocols that use specific Finnegan scores to initiate therapy are based on precedent but not on evidence.

However, adopting a protocol and adhering to it reduces the length of hospital stay.
CLONIDINE vs. PHENOBARB AS ADJUNCT

Unblinded study of morphine plus clonidine vs. morphine plus phenobarbital (34 infants in each group)

Primary outcome: days of morphine therapy

Protocol: Clonidine weaned in hospital but infants could be discharged home on phenobarbital

Results: Phenobarbital continued for mean of 3.8 (range, 1-8) months

<table>
<thead>
<tr>
<th></th>
<th>CLONIDINE</th>
<th>PHENOBARBITAL</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of morphine</td>
<td>18.2</td>
<td>13.6</td>
<td>0.037</td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td>5.7</td>
<td>4.6</td>
<td>0.069</td>
</tr>
</tbody>
</table>

METHADONE PHARMACOKINETICS

OTHER ISSUES

Breast feeding

Hospital rooming-in
• Facilitate rooming-in by parents, caregivers
• Encourage breast feeding
• Minimize pharmacologic treatment
• Tolerate higher NAS scores: goal is not to eliminate signs!

Outpatient management
• Occurs in some areas of the country by necessity
• Literature (much is European) documents excessive lengths of treatment; high use of phenobarbital
• Requires excellent family selection and close follow-up: only takes one serious morbidity to dismantle a program
• Two “recent” reported experiences (Australia; Ohio)
SUMMARY POINTS ABOUT TREATMENT

Substantial variability in resources for non-pharmacologic treatment

Significant variability in NAS assessment and criteria to initiate pharmacologic treatment

Existing data are insufficient to identify optimal initial drug treatment

Optimal adjunctive therapy remains controversial

Having a treatment/weaning protocol decreases LOS

Improved assessment of integrated prenatal drug exposure may allow tailoring of postnatal treatment

Analysis of genetic and epigenetic information may identify babies at highest risk for severe withdrawal
QUESTIONS