Neonatal Abstinence Syndrome (NAS)

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Program for HealthTrust Members
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- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
Learning Objectives

1. Define the mechanism and clinical presentation of NAS
2. List advantages and limitations of assessment tools utilized for NAS
3. Recognize recommended treatment options for NAS
4. Discuss adjunctive therapies used for NAS
5. State important safety and efficacy parameters associated with the treatment options
Background

- Withdrawal symptoms in newborns due to the combination *in utero* exposure and postnatal cessation
- Sudden discontinuation of prolonged fetal exposure
- Incidence has increased significantly in the past decade
  - Proportionate with the increased use of opioids during pregnancy
- Opioid use antepartum is the most common cause of NAS

## Major Drugs of Abuse

<table>
<thead>
<tr>
<th>Opioids</th>
<th>CNS† Stimulants</th>
<th>CNS Depressants</th>
<th>Hallucinogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Amphetamines</td>
<td>Alcohol</td>
<td>Indolealkylamines (e.g. LSD*)</td>
</tr>
<tr>
<td>Codeine</td>
<td>Methylphenidate</td>
<td>Barbiturates</td>
<td>Phenylisopropylamines (e.g. MDMA**)</td>
</tr>
<tr>
<td>Methadone</td>
<td>Phentermine</td>
<td>Benzodiazepines</td>
<td>Nitrates</td>
</tr>
<tr>
<td>OxyCODONE</td>
<td>Cocaine</td>
<td>Cannaboids</td>
<td>Nitrous Oxide</td>
</tr>
<tr>
<td>HYDROMorphone</td>
<td>Nicotine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYDROcodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TraMADol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LSD = lysergic acid diethylamide; **MDMA = 3,4-methylenedioxyamphetamine; †CNS = central nervous system

Risk of Withdrawal

- Type and dose of opioid
- Timing and duration of exposure
- Maternal risk factors
- Placental opioid metabolism
- Genetic variables
- Neonatal conditions
- Environmental factors
Outcomes of Maternal Opioid Use

- **Fetus**
  - Growth restriction
  - Preterm labor
  - Abnormal heart patterns
  - Death

- **Newborn**
  - Low birth weight
  - Preterm delivery
  - Small head circumference
  - Sleep myoclonus
  - Child maltreatment
  - Visual disturbances

Outcomes of NAS

- Increased risk of birth complications
- Admission to neonatal intensive care unit (NICU)
- Pharmacologic treatment
- Prolonged hospitalization
- Infant development
- Child-safety concerns

Opioids in Pregnancy

- Lower molecular weight
- Lipophilic substances
- Easily transferable across the placenta
  - Transmission increases with gestation
- Easily transferable across the blood-brain barrier
- Synthetic opioids cross the placenta more easily compared to semisynthetic opioids

Mechanism of Withdrawal

- Fetal drug exposure
- Tolerance: increased noradrenaline release
- Abrupt discontinuation: increased release of noradrenaline
- Autonomic and behavioral signs and symptoms
- Withdrawal

# Clinical Manifestations

<table>
<thead>
<tr>
<th>Autonomic/vasomotor/respiratory</th>
<th>Gastrointestinal</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Projectile vomiting</td>
<td>Tremors</td>
</tr>
<tr>
<td>Sweating</td>
<td>Regurgitation</td>
<td>High-pitched crying</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>Loose/watery stools</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>Mottling</td>
<td>Weight loss</td>
<td>Increased muscle tone</td>
</tr>
<tr>
<td>Tachypnea with or without retractions</td>
<td>Poor feeding/sucking</td>
<td>Frequent yawning/sneezing</td>
</tr>
<tr>
<td></td>
<td>Excessive sucking</td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myoclonic jerks</td>
</tr>
</tbody>
</table>

## Timing of Withdrawal

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>24 to 48 hours</td>
</tr>
<tr>
<td>Opioids</td>
<td>48 to 72 hours</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>36 to 60 hours</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>1 to 14 days</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Hours to weeks</td>
</tr>
<tr>
<td>SSRIs*</td>
<td>24 to 48 hours</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>24 hours</td>
</tr>
<tr>
<td>Cocaine</td>
<td>48 to 72 hours</td>
</tr>
<tr>
<td>Nicotine</td>
<td>24 to 48 hours</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3 to 12 hours</td>
</tr>
</tbody>
</table>

*SSRI = selective serotonin reuptake inhibitor

Assessment

- Determine severity of signs and symptoms
- Provide guidance for pharmacologic therapy
- Facilitate weaning
- Withdrawal scoring systems
  - Finnegan Scoring Tool
    - The Neonatal Abstinence Scoring System
  - Lipsitz Scoring Tool
    - The Neonatal Drug Withdrawal Scoring System
  - Modified Finnegan Scoring Tool
    - MOTHER NAS Scale

## Finnegren Scoring Tool

<table>
<thead>
<tr>
<th>System</th>
<th>Signs and Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic/vasomotor/respiratory</td>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fever &lt; 101°F (39.3°C)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fever &gt; 101°F (39.3°C)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Frequent yawning</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 to 4 times/interval)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nasal flaring</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate &gt; 60 breaths/min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate &gt; 60 breaths/min with retractions</td>
<td>2</td>
</tr>
</tbody>
</table>
## Finnegan Scoring Tool

<table>
<thead>
<tr>
<th>System</th>
<th>Signs and Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</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>
</tbody>
</table>
## Finnegan Scoring Tool

<table>
<thead>
<tr>
<th>System</th>
<th>Signs and Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High pitched cry</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Continuous high pitched cry</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 1 hour after feeding</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 2 hours after feeding</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 3 hours after feeding</td>
<td>1</td>
</tr>
<tr>
<td>Central Nervous</td>
<td>Hyperactive Moro reflex</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Markedly hyperactive Moro reflex</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild tremors disturbed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe tremors disturbed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild tremors undisturbed</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe tremors undisturbed</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mild increased muscle tone</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Excoriation (specific area)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Myoclonic jerks</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Generalized convulsions</td>
<td>3</td>
</tr>
</tbody>
</table>

# Lipsitz Scoring Tool

<table>
<thead>
<tr>
<th>Signs</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremors (muscle activity of limbs)</td>
<td>Normal</td>
<td>Minimally increased when hungry or disturbed</td>
<td>Moderate/marked increase when undisturbed; stop when fed or cuddled</td>
<td>Marked increase or continuous even when undisturbed; going on to seizure-like movements</td>
</tr>
<tr>
<td>Irritability (excessive crying)</td>
<td>None</td>
<td>Slightly increased</td>
<td>Moderate to severe irritability when disturbed or hungry</td>
<td>Marked irritability even when undisturbed</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
<td>Increased</td>
<td>Markedly increased</td>
<td></td>
</tr>
<tr>
<td>Stools</td>
<td>Normal</td>
<td>Explosive, but frequency ≤ 8/day</td>
<td>Explosive; &gt; 8/day</td>
<td></td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Normal</td>
<td>Increased</td>
<td>Rigidity</td>
<td></td>
</tr>
<tr>
<td>Skin Abrasions</td>
<td>No</td>
<td>Redness of elbows, heels, pressure points when supine</td>
<td>Breakdown of skin at pressure points</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate (bpm)</td>
<td>&lt; 55</td>
<td>55 to 75</td>
<td>76 to 95</td>
<td></td>
</tr>
<tr>
<td>Repetitive Sneezing</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetitive Yawning</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceful Vomiting</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever &gt; 38°C or &gt;100.4°F</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>17</strong></td>
</tr>
</tbody>
</table>
## Withdrawal Scoring Systems

<table>
<thead>
<tr>
<th>Tool (year)</th>
<th>No. of Items</th>
<th>Score Range</th>
<th>Score for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnegan Neonatal Abstinence Scoring Tool (1975)</td>
<td>21</td>
<td>0 to 62</td>
<td>≥ 8 on three consecutive evaluations</td>
</tr>
<tr>
<td>Lipsitz Neonatal Drug Withdrawal Scoring System (1975)</td>
<td>11</td>
<td>0 to 20</td>
<td>≥ 4</td>
</tr>
<tr>
<td>MOTHER NAS Scale (2010)</td>
<td>19</td>
<td>0 to 42</td>
<td>9; rescore before initiation of drug treatment</td>
</tr>
<tr>
<td>Finnegan Neonatal Abstinence Syndrome Scale – Short Form (2013)</td>
<td>7</td>
<td>0 to 16</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>
## Withdrawal Scoring Systems

<table>
<thead>
<tr>
<th>Tool (year)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Finnegan Neonatal Abstinence Scoring Tool (1975) | - Most commonly utilized scoring tool  
- Lengthy/complex  
- Less practical  
- Internal consistency |
| Lipsitz Neonatal Drug Withdrawal Scoring System (1975) | - Simplistic/sensitive  
- Does not address reliability  
- No item definitions provided |
| MOTHER NAS Scale (2010) | - Modified version of Finnegan Scoring Tool  
- Proper instructions  
- Protocol for pharmacologic treatment  
- More practical  
- Internal consistency |
| Finnegan Neonatal Abstinence Syndrome Scale – Short Form (2013) | - Rapid assessment  
- Limited items  
- Strong correlation with original Finnegan Scoring Tool  
- Inadequate for rapidly escalating signs and symptoms  
- Requires further testing |
Supportive Care Treatment

- Swaddling and/or rocking
- Minimizing sensory and/or environmental stimulation
- Music and massage therapy
- Temperature stability
- Breastfeeding and frequent feeds

Pharmacologic Treatment

- Drug withdrawal is a self-limiting process

- Indications
  - Newborns at high risk of withdrawing
    - Score > 8 on the Finnegan Scoring System
    - Score > 4 on Lipsitz Tool
  - Newborns who failed supportive care treatment

- Purpose
  - Relieve moderate to severe signs of NAS
  - Prevent complications
  - Provide comfort

Pharmacologic Treatment

- No universally accepted standard of care
  - Dose based on weight vs severity of symptoms
  - Threshold for initiating treatment
  - Starting doses
  - Weaning protocols
  - Adjunctive medications

- Advantage
  - Short term improvement of clinical signs

- Limitations
  - Prolong drug exposure
  - Prolong duration of hospitalization
  - Decrease maternal-infant bonding

Patient Case

Baby girl born at 39 + 3 weeks gestational age; 2495 grams

**Maternal History**
- History of opioid abuse
- GBS positive
- HIV, Rubella, RPR, HBsAG negative

**Maternal Medications**
- Folic acid, prenatal vitamins, morphine

**Delivery History**
- Intrapartum cefazolin 2 gm IV once
Patient Case

Vitals
- Heart rate: 170 beats/min
- Blood pressure: 57/26 mmHg
- Respiratory rate: 66 breaths/min
- Temperature: 37.8°C

Physical Exam
- Neuro: mild tremors, undisturbed
- Heart: tachycardic
- Lungs/thorax: tachypneic
- HEENT: within normal limits
- Activity and reflexes: markedly hyperactive Moro reflex
- Skin: sweating

Should pharmacologic treatment be started?
Pharmacologic Therapies

- Paregoric
- Tincture of opium
- Morphine
- Methadone
- Buprenorphine
- Adjunctive agents
  - PHENobarbital
  - CloNIDine
  - Benzodiazepines
    - Diazepam, LORazepam
  - ChlorproMAZINE

Paregoric

- Earliest opioid used
- Anhydrous morphine available as 0.4 mg/mL
- Decreases neuronal activity
- No longer recommended
  - Noscapine, papaverine, camphor, ethanol, anise oil, benzoic acid, and glycerin

Tincture of Opium

- Contains 10 mg/mL opium
- Contains fewer toxic additives than paregoric
- Institute for Safe Medication Practice (ISMP) safety alerts
  - Contains ethanol
  - Contains multiple narcotic alkaloids
  - Dilution required to produce 0.4 mg/mL morphine equivalence
- Not commonly used

Morphine

- Most frequently used agent
- Mu-opioid receptor agonist
- Short half-life
- Oral solution
  - Dilution to 0.4 mg/mL recommended
- ISMP safety alert
- Advantages
  - Easily titratable
  - No ethanol
- Limitations
  - Increased risk of sedation, respiratory depression, and constipation
  - Prolonged hospital stay
Methadone

- Alternative to morphine
- Mu-opioid receptor agonist and NMDA receptor antagonist
- Long half-life; variable

**Advantages**
- No dilution required
- Consistent blood concentration
- Less frequent dosing

**Limitations**
- Risk of drug accumulation
- Prolonged hospital stay
- Contains ethanol

Back to the Patient

Despite optimal supportive care, the next Finnegan Score was 10. The plan for the newborn is to start on morphine therapy to help with her NAS.

Weight = 2.495 kg

Recommended dosing:
- Morphine 0.05 mg/kg/dose po every 3 hours
- Morphine 0.125 mg po every 3 hours
Buprenorphine

- Newer option
- Partial mu-opioid receptor agonist
- Given sublingually
  - Intravenous injection
  - Sublingual tablet
  - Compounded to an extemporaneous oral solution
    - 75 mcg/mL

- Advantages
  - Shorter duration of treatment

- Limitations
  - Contains ethanol

Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

- **Objective**: to determine duration of treatment in infants with NAS comparing sublingual buprenorphine with oral morphine
- **Design**: prospective, double-blind, double-dummy, single center, randomized clinical trial
- **Interventions**
  - Sublingual buprenorphine (n = 33): 0.075 mg/mL
  - Oral morphine (n = 30): dose based on the center standard-of-care morphine protocol
  - PHENobarbital; provided if given maximum dose of opioid reached
    - Loading dose: 20 mg/kg po
    - Maintenance dose: 5 mg/kg po daily

Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

- **Primary outcome**: duration of treatment
- **Secondary outcomes**
  - Length of hospital stay
  - Use of adjunct PHENobarbital
  - Adverse events

Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

- **Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Buprenorphine (n = 33)</th>
<th>Morphine (n = 30)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of treatment; days</td>
<td>15</td>
<td>28</td>
<td>-13 (-21 to -7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Median length of hospital stay; days</td>
<td>21</td>
<td>33</td>
<td>-12 (-22 to -7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Use of adjunct PHENobarbital; n (%)</td>
<td>5 (15)</td>
<td>7 (23)</td>
<td>---</td>
<td>0.36</td>
</tr>
<tr>
<td>Adverse events</td>
<td>13 events in 7 patients</td>
<td>10 events in 8 patients</td>
<td>---</td>
<td>0.79</td>
</tr>
</tbody>
</table>

- **Conclusion**
  - Not completely clear how buprenorphine allows for shorter duration of treatment than morphine

PHENobarbital

- Non-opioid drug of choice
- Enhances gamma-amino butyric acid (GABA)
  - CNS depression
- Long acting barbiturate
- Monotherapy or adjunct therapy
- Advantages
  - Adjuvant in those withdrawing from poly drug abuse
  - Lower doses of morphine or methadone
- Limitations
  - Does not prevent seizures
  - Ineffective for gastrointestinal symptoms
  - Central nervous system depression
  - Impairment of sucking reflex
  - Cognitive impairment
  - Contains ethanol (unless compounded from tablets)
**CloNIDine**

- Centrally acting $\alpha_2$-adrenergic receptor agonist
- Adjunct therapy
- **Advantages**
  - Adjuvant in those withdrawing from poly-drug abuse
  - Shorter duration of treatment
  - Lower doses of morphine or methadone
- **Limitations**
  - Risk of hypotension and bradycardia
  - Must be weaned off slowly

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CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- **Objective**: to compare the efficacy of cloNIDine versus PHENobarbital in reducing morphine sulfate treatment days for NAS
- **Design**: prospective, non-blinded, single center, randomized clinical trial
- **Interventions**
  - Morphine sulfate + cloNIDine (n = 34)
  - Morphine sulfate + PHENobarbital (n = 34)
  - Dosing protocol utilized
    - Based on Finnegan Score
CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- **Primary outcome**: treatment days with morphine sulfate
- **Secondary outcomes**
  - Mean total morphine sulfate dose
  - Outpatient PHENobarbital days
  - Adverse events
  - Treatment failure
  - Mortality in the hospital
  - Readmission within 1 week post discharge
CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

### Results

<table>
<thead>
<tr>
<th>Univariable</th>
<th>PHENobarbital (n = 34)</th>
<th>CloNIDine (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate; days (95% CI)</td>
<td>12.4 (10.1 to 14.7)</td>
<td>19.5 (15.7 to 23.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean total morphine sulfate dose; mg/kg (95% CI)</td>
<td>3.8 (2.9 to 4.7)</td>
<td>6.7 (5.1 to 8.3)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

## CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

### Results continued

<table>
<thead>
<tr>
<th>Multivariable</th>
<th>PHENobarbital (n = 34)</th>
<th>CloNIDine (n = 34)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate; days (95% CI)</td>
<td>13.6 (11.0 to 16.1)</td>
<td>18.2 (14.9 to 21.5)</td>
<td>0.037</td>
</tr>
<tr>
<td>Mean total morphine sulfate dose; mg/kg (95% CI)</td>
<td>4.6 (3.8 to 5.4)</td>
<td>5.7 (4.7 to 6.8)</td>
<td>0.069</td>
</tr>
</tbody>
</table>

CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- **Results continued**
  - Post-discharge PHENobarbital was continued for an average of 3.8 months (range 1 to 8 months)
  - No difference in adverse events
  - No difference in treatment failure
  - No inpatient mortality
  - No readmission within 1 week post discharge

- **Conclusion**
  - PHENobarbital as an adjunct shortened length of inpatient treatment days with morphine compared to cloNIDine
  - Overall length of NAS treatment is shorter with cloNIDine since no outpatient treatment is required
Morphine versus CloNIDine for Neonatal Abstinence Syndrome

- **Objective**: to determine whether cloNIDine treatment for NAS would result in better neurobehavioral performance compared to morphine
- **Design**: randomized, double-blind trial
- **Interventions**
  - Morphine (n = 15)
    - Starting dose of 0.4 mg/kg/day po q3h
  - CloNIDine (n = 16)
    - Starting dose of 5 mcg/kg/day po q3h
Morphine versus Clonidine for Neonatal Abstinence Syndrome

- **Outcomes**
  - Neurobehavioral performance
    - Measured via the NICU Network Neurobehavioral Scale (NNNS)
      - NNNS administered at 1 week and 2 to 4 weeks after treatment initiation
  - Inpatient treatment duration
  - Outpatient treatment duration

Morphine versus CloNIDine for Neonatal Abstinence Syndrome

- **Results**
  - No difference in NNNS scores between morphine and cloNIDine at 1 week and 2 to 4 weeks after treatment initiation
  - Morphine-treated infants showed no difference in any areas from the first to the second assessment
  - CloNIDine-treated infants showed significant improvement in areas of attention, handling, arousing, excitability, and lethargy from the first to the second assessment

Morphine versus CloNIDine for Neonatal Abstinence Syndrome

- **Results**
  - Significant difference in duration of inpatient treatment

<table>
<thead>
<tr>
<th></th>
<th>Morphine (n = 15)</th>
<th>CloNIDine (n = 16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range); days</td>
<td>39 (26 to 89)</td>
<td>27.5 (18 to 107)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Significant difference in duration of outpatient treatment

<table>
<thead>
<tr>
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<th>CloNIDine (n = 16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range); days</td>
<td>26 (16 to 57)</td>
<td>13.5 (6 to 71)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- **Conclusion**
  - Use of cloNIDine as monotherapy may be considered
  - Larger randomized clinical trials are needed

Benzodiazepines

- GABA receptor agonist
- Long half-life
- Limitations
  - Central nervous system depression
  - Impairment of sucking reflex
  - Lack of efficacy
  - Safety issues
  - Side effects
- Not recommended
Chlorpromazine

- Phenothiazine antipsychotic; dopamine receptor antagonist
- Long half-life
- Limitations
  - Central nervous system depression
  - Impairment of sucking reflex
  - Lack of efficacy
  - Safety issues
  - Side effects
- Not recommended
## Pharmacologic Therapy Protocols

<table>
<thead>
<tr>
<th></th>
<th>Hall et al.</th>
<th>Patrick et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To identify pharmacologic treatment strategies for NAS associated with optimal short-term outcomes</td>
<td>To evaluate if standardized care for infants with NAS was associated with improved outcomes</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Multicenter, cohort analysis, n = 547</td>
<td>Multicenter, cohort analysis, n = 3458</td>
</tr>
<tr>
<td><strong>Intervention(s)</strong></td>
<td>Presence of established NAS weaning protocol arm (n = 130)</td>
<td>Adaptation of standardized institutional policy for NAS (n = 3458)</td>
</tr>
<tr>
<td></td>
<td>Absence of established NAS weaning protocol arm (n = 417)</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Opioid treatment duration</td>
<td>Length of treatment</td>
</tr>
<tr>
<td></td>
<td>Length of stay</td>
<td>Hospital length of stay</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Significantly shorter: Duration of opioid treatment; (17.7 vs 32.1 days, p &lt; 0.001)</td>
<td>NAS-focused policies increased; 3.7 to 5.1 (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>Length of stay</td>
<td>Decreased length of treatment; 16 to 15 days (p = 0.02)</td>
</tr>
<tr>
<td></td>
<td>(22.7 vs 32.1 days, p = 0.004)</td>
<td>Decreased hospital length of stay; 21 to 19 days (p = 0.002)</td>
</tr>
</tbody>
</table>
Morphine versus CloNIDine for Neonatal Abstinence Syndrome Weaning Protocol

- Finnegan Scoring Tool
- Morphine was increased by 25% of the initial dose every 24 hours until scores were < 8 and symptoms were controlled
  - Maximum dose of 1 mg/kg/day
- After 48 hours of symptom control, all scores < 8, morphine was decreased by 10% once every other day
- Once the dose was < 0.1 mg/kg/day, morphine was discontinued
- Observed for 48 hours after the last dose of trial medication
- If symptoms recurred, previous dose was administered
  - Weaning resumed after 48 hours
Back to the Patient

Newborn improved symptomatically over the next 36 to 48 hours.

**Vitals**
- Heart rate: 100 beats/min
- Blood pressure: 60/29 mmHg
- Respiratory rate: 50 breaths/min
- Temperature: 37.0°C

**Physical Exam**
- Neuro: mild tremors, disturbed
- Heart: within normal limits
- Lungs/thorax: within normal limits
- HEENT: within normal limits
- Activity and reflexes: hyperactive moro reflex
- Skin: within normal limits

How should the patient be weaned off of morphine?
Follow-up

- Psycho-behavioral assessment
  - Hyperactivity, impulsivity, and attention-deficit
- Ophthalmologic assessment
  - Nystagmus, strabismus, visual deficits
- Growth and nutritional assessment
- Family support assessment
Long-term Outcomes

- Difficult to evaluate
  - Confounding variables
- At risk of motor deficits, cognitive delays, or relative microcephaly
Summary

- Implementation of a standardized protocol at each institution is the optimal way to approach pharmacologic treatment for patients with NAS

- Buprenorphine is an emerging new therapy that may be considered for first line treatment for patients with NAS

- Larger randomized clinical trials need to be conducted to determine the role of clonidine as monotherapy

- Important safety and preparation considerations associated with pharmacologic therapy when treating patients with NAS
Poll Question #1

1. Signs and symptoms of NAS may be classified by the following affected systems except:
   a. Neurologic
   b. Renal
   c. Gastrointestinal
   d. Autonomic
Response Question #1

1. Signs and symptoms of NAS may be classified by the following affected systems except:
   a. Neurologic
   b. Renal
   c. Gastrointestinal
   d. Autonomic
Poll Question #2

2. The Finnegan Scoring System has ___ main categories and ___ variables
   a.  3, 12
   b.  3, 21
   c.  12, 3
   d.  21, 3
Response Question #2

2. The Finnegan Scoring System has ___ main categories and ___ variables
   a. 3, 12
   b. 3, 21
   c. 12, 3
   d. 21, 3
Poll Question #3

3. Which of the following is most frequently used for the treatment of NAS
   a. Morphine
   b. Methadone
   c. Buprenorphine
   d. CloNIDine
Response Question #3

3. Which of the following is most frequently used for the treatment of NAS
   
   a. Morphine
   b. Methadone
   c. Buprenorphine
   d. CloNIDine
Poll Question #4

4. A disadvantage of using cloNIDine for adjunctive treatment is
   a. Only available in oral formulation
   b. Does not exhibit the sedative or respiratory depressive properties of opioid or barbiturate agents
   c. Lowers blood pressure
   d. Contains alcohol
Response Question #4

4. A disadvantage of using clonidine for adjunctive treatment is
   a. Only available in oral formulation
   b. Does not exhibit the sedative or respiratory depressive properties of opioid or barbiturate agents
   c. Lowers blood pressure
   d. Contains alcohol
Poll Question #5

5. Which of the following must be monitored in neonates while on morphine therapy for NAS
   a. Sedation
   b. Respiratory depression
   c. Constipation
   d. All of the above
Response Question #5

5. Which of the following must be monitored in neonates while on morphine therapy for NAS
   a. Sedation
   b. Respiratory depression
   c. Constipation
   d. All of the above
Thank you...