Preventing Neonatal Opioid Withdrawal: A Palliative Model

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Disclosures

- I have no financial dualities of interest or relevant relationships to disclose

Objectives

- Review national and regional trends related to neonatal abstinence syndrome
- Review examples of existing efforts to identify and treat NAS in the US and in other countries
- Discuss the benefits and safety profile of a model of early treatment for neonatal opioid withdrawal in term infants
What We Really Hope You Hear

- Suffering is cruel and unnecessary
- Newborns deserve early and effective treatment for opioid withdrawal, just as they do for pain
- Our early treatment model is safe, effective, cost-saving and feasible for hospitals to consider replicating

Background

- Prescription drug misuse is our nation’s fastest growing drug problem
- Opiate use in women of reproductive age is rising
  - 5-fold increase in use by pregnant mothers
  - 30% of young Medicaid women have a current opiate prescription

Current Trends

- Prescription drug misuse
  - 5.3M painkiller prescriptions/month
  - Increase of 48% in past decade
  - Costs to healthcare and society rising exponentially (2001: $8.6B)
Current Clinical Challenges

- A majority of birthing centers are not skilled in detecting or treating NAS
  - Lack of knowledge about which newborns are at risk
  - Nonspecific symptoms are easy to misinterpret
  - Pressure to achieve short length of stay

- Observation and treatment protocols vary by institution, state, and country
  - No formal guidelines for overall management of NAS
  - No agreement about which abstinence scoring system should be the “gold standard”
  - Several medications are available to treat, but no standard dosing approach or clinical care guidelines yet exist in the US

Newborns are Dependent, not Addicted

Definitions

- **Addiction** – chronic behavioral disease characterized by one or more of the following “three Cs”
  - Compulsive drug use
  - Continued use despite harm
  - Craving

- **Dependence** – a state of adaptation characterized by a withdrawal syndrome upon abrupt cessation or rapid wean

- **Tolerance** – the quality of requiring a larger amount of a drug over time to achieve the same desired effect
Pop Quiz

• How do most physicians learn to manage neonatal abstinence syndrome?

A. Medical school
B. National conferences
C. Formal professional guidelines
D. Trial and error

Background

• Hospital costs are rising
  - $66,700 per withdrawing newborn
  - $93,400 per pharmacologically-treated newborn
  - 78% Medicaid-funded

Why Focus on NAS

• Demand for and costs associated with maternal-newborn services are already high

• Rising rates of NAS will escalate strain on state Medicaid costs, especially if escalating numbers are cared for in Level II-IV settings

• NAS is a marker for long-term family issues
  - Chronic drug use is linked to crime, incarceration, child neglect and abuse
  - 6M children (9% in US) live with at least one parent who abuses drugs or alcohol
  - Toxic social and physical environments (stressors)
  - Risk for behavioral problems, developmental delays, educational neglect
  - Potential for addiction later in life
Why Focus on NAS

- Pregnancy provides a “window of opportunity” for women to engage in lifestyle changes
- We can empower parents struggling with addiction in order to
  - Improve family success
  - Promote change and healthy choices
  - Support family planning and healthy future pregnancies
  - Reduce rates of child neglect and abuse, foster care

Kiko, Greenville Zoo, 2013

Tennessee

Just flooding us: Tenn. spike in drug-dependent newborns is warning to nation

NAS in TN: 1999-2010

Drug Dependant Newborns (Neonatal Abstinence Syndrome)
Surveillance Summary For the Week of December 27, 2015 - January 2, 2016

2015 case rate exceeds prior years
Nationwide Children’s QI project to decrease length of stay for NAS in NICUs statewide

2009: 58 days
2011: 24 days
Goal: 18 days
**NAS in South Carolina**

**Growing Concerns**
- Hospital admissions (premature or NAS)—highly associated with newborns affected by prenatal drug exposure or withdrawal during pregnancy.
- U.S. rate of babies born with NICU per 1,000 hospital births.

**Mean SC Hospital Charges (All Payers) per NAS Birth, 2014**
- Overall: $60,176
- In NICU: $157,912
- Total: $24,250,928

**Source of Data:**
- South Carolina Office of Research and Statistics
- Division of Research and Statistics
- UB-04 Hospital Billing Data

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**Greenville Memorial Hospital**

- Level IV Perinatal Care Center
- 5,600 deliveries annually
- 88% of births – Mom/Baby care
- 85-bed NICU
- Baby-Friendly designated

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**Our Patients**

- 29yo G1 mother
- Adverse childhood experiences:
  - Physical, sexual, emotional abuse
- Mental health history:
  - Anxiety, depression, PTSD, psych admission age 16
- Drug screens:
  - Positive for THC, benzo, opioids for 10 years and in third trimester, but negative at delivery
- Inadequate PNC:
  - 6 visits, left one without being seen
  - admits using inoxodone and hydrocodone during pregnancy
  - would take it daily if she could get it
  - took methadone 4 months during pregnancy and quit
- In hospital:
  - Denies current use, last oxycodone “2 weeks ago”
Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate.

- A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain.
- Exposure to prolonged or severe pain may increase neonatal morbidity.
- Infants who have experienced pain during the neonatal period respond differently to subsequent painful events.
- Neonates are not easily comforted when analgesia is needed.

**AAP Guidance**

**Stance on Pain**

When pain is prolonged, striking changes occur in the infant’s physiologic and behavioral indicators.

The prevention of pain in neonates should be the goal of all caregivers, because repeated painful exposures have the potential for deleterious consequences.

**Stance on Withdrawal**

...the severity of withdrawal signs, including seizures, has not been proven to be associated with differences in long-term outcome after intrauterine drug exposure. Ultimately, withdrawal is a self-limited process.

Treatment of drug withdrawal may not alter the long-term outcome.

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AAP Committee on Fetus and Newborn. Prevention and Management of Pain and Stress in the Neonate. Pediatrics, 2000

AAP Committee on Drugs and Committee on Fetus and Newborn. Neonatal Drug Withdrawal. Pediatrics, 2012

AAP Committee on Fetus and Newborn. Prevention and management of pain and stress in the neonate. Pediatrics, 2000

Prevention and management of pain in the neonate: an update. AAP Committee on Fetus and Newborn and Section on Surgery, Section on Anesthesiology and Pain, Committee on Drugs, Canadian Paediatric Society, Fetus and Newborn Committee. Pediatrics, 2004
Withdrawal is…

- Stage I: craving, anxiety, irritability, perspiration
- Stage II: add yawning, lacrimation, rhinorrhea, depression
- Stage III: add dilated pupils, pilo-erection (cold turkey), hot/cold flashes, aches, cramps, anorexia
- Stage IV: add severe cramping, involuntary leg movements (kicking the habit), loose stool, hypertension, tachypnea, tachycardia, hyperthermia, nausea, restlessness
- Stage V: add fetal position, vomiting, profuse liquid diarrhea, leukocytosis, weight loss of 4-12 pounds per day
- Stage VI: transition to normalizing bowel function but ongoing psychologic symptoms, hypersensitivity to pain, prolonged hypertension, weight control issues

Early Treatment Concept

- 55-94% of term newborns with chronic fetal exposure to long-acting opioids develop withdrawal
- Delaying treatment seems to…
  - Result in difficulty gaining symptom control
  - Lead to excessive weight loss and abnormal suck patterns
  - Exacerbate self-inflicted skin injuries and diaper rash
  - Increase risk of seizures and fever
  - Be cruel and unethical
- Early treatment with low-dose methadone can be considered a continuation of therapy and might…
  - Prevent full-blown symptoms and their complications
  - Reduce weight loss levels
  - Improve parental engagement and lessen feelings of guilt
  - Result in a shorter length of stay than “last resort” treatment
  - Therefore, result in lower health care costs

Palliative Hypothesis

- With an outpatient partner, newborns might be safely weaned at home
Research Objective

To describe health outcomes and hospital costs for newborns with NAS who were treated using an early pharmacologic treatment model in a low-acuity care setting, with outpatient weaning.

Study Population

Target population: All babies born at Greenville Memorial Hospital and coded for NAS diagnosis between 2006 and 2014

- Inclusion criteria
  - Newborns admitted to GMH level I nursery care
  - Long-acting opioid-exposed (methadone or buprenorphine)
  - Treated with early low-dose methadone therapy (within first 24 hours)

- Exclusion criteria
  - NICU admission prior to initiation of medication

- Final sample size: 147 treated newborns
  - 30 (20%) transferred to NICU for medical complication (seizure, fever, arrhythmia)
  - 117 (80%) treated with complete palliative model

Palliative (Early Treatment) Model

- Otherwise healthy newborn identified with chronic fetal exposure to methadone or buprenorphine
- H&P completed; routine and protocol orders initiated after discussion with family, unless family is averse to pharmacological treatment

- Protocol orders:
  - Start methadone: 0.05mg/kg/dose po q6h for maternal buprenorphine use or low-dose (<60mg daily) methadone use; 0.1mg/kg/dose po q6h for high-dose methadone use
  - Consults to social services/case management, physical and occupational therapy, pediatric pharmacy
  - Urine and meconium drug screens
  - Apnea/bradycardia monitoring in mother’s room
  - Modified Finnegan abstinence scoring every 4 hours
  - Encourage breastfeeding unless contraindicated
  - Barrier cream to perianal skin as needed
**Palliative (Early Treatment) Model**

- **Stabilization:** monitor for evidence of
  - Under-treatment (high scores, weight loss, exam intolerant, feeding problems)
  - Stability (stable scores at or under 8, gaining weight, exam tolerant)
  - Over-sedation (very low scores, bradypnea/bradycardia alarms, difficulty awakening)
- Solicit feedback from care team daily: family, nurses, therapists, pharmacist
- Increase methadone in 0.05mg/kg increments (if needed), ideally once per day
  - Hold methadone, with input from pharmacy, if over-sedated
- **After 36-48h of stability, spread (don’t wean) dosing
  - First spread: 24-hour dose divided q8h
  - Wait 36-48h, then second spread: 24-hour dose divided q12h
  - Wait 36-48h to ensure ongoing stability prior to discharge
- **Day before expected discharge:** develop weaning calendar and write rx
  - Fill in hospital outpatient pharmacy pre-filled oral syringes
  - Maximum 30-day wean allows entire rx to be dispensed
  - Wean every Sunday and Wednesday
  - PCP visits weekly on Mondays or Thursdays until wean done
  - Filled rx is reconciled by unit staff; calendar and medication reviewed with family

**Methods and Measures**

- Retrospective Chart Review
- **Primary Outcome Measures**
  - Hospital length of stay
  - Need for adjunctive medication
  - Peak abstinence score and weight loss
  - Medical complications requiring transfer to the neonatal intensive care unit (NICU)
  - Adverse medication and safety events
    - Infant drops, unsafe sleep, over-sedation during treatment
  - Emergency department utilization within 30 days of discharge
  - Total hospital charges and cost per case
Maternal Demographics (N = 117)

<table>
<thead>
<tr>
<th>Age</th>
<th>35 +/- 5 years</th>
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<tbody>
<tr>
<td>Caucasian race</td>
<td>90%</td>
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<tr>
<td>Education level</td>
<td></td>
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<tr>
<td>&lt; 12 years</td>
<td>28%</td>
</tr>
<tr>
<td>High school degree</td>
<td>35%</td>
</tr>
<tr>
<td>Some college or associates degree</td>
<td>37%</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
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<tr>
<td>Married/separated</td>
<td>37%</td>
</tr>
<tr>
<td>Never married</td>
<td>63%</td>
</tr>
<tr>
<td>Received prenatal care</td>
<td>96%</td>
</tr>
<tr>
<td>(Mean number of prenatal visits 8.3 with SD 3.9)</td>
<td></td>
</tr>
<tr>
<td>Mental health issues (Not mutually exclusive)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>64%</td>
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<tr>
<td>Anxiety</td>
<td></td>
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<tr>
<td>Bipolar disorder</td>
<td>13%</td>
</tr>
<tr>
<td>Clinical level</td>
<td></td>
</tr>
<tr>
<td>Methadone (Mean dose 96.2 mg/day)</td>
<td>70%</td>
</tr>
<tr>
<td>Buprenorphine (Mean dose 12.9 mg/day)</td>
<td>30%</td>
</tr>
<tr>
<td>Tobacco use during pregnancy</td>
<td>72%</td>
</tr>
<tr>
<td>CPS involved</td>
<td></td>
</tr>
<tr>
<td>Ante- or peri-</td>
<td>20%</td>
</tr>
<tr>
<td>natal discharge</td>
<td>21%</td>
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<tr>
<td>No involvement</td>
<td>59%</td>
</tr>
<tr>
<td>Feeding method</td>
<td></td>
</tr>
<tr>
<td>Exclusive breast milk</td>
<td>8%</td>
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<tr>
<td>Exclusive formula</td>
<td>63%</td>
</tr>
<tr>
<td>Mixed breast/formula</td>
<td>31%</td>
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<tr>
<td>Overall breastfeeding rate</td>
<td>8%</td>
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<tr>
<td>Gestational age 38.5 weeks (range: 35-41)</td>
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<tr>
<td>Peak on-Finnegan abstinence score 10 (peak on day 2)</td>
<td></td>
</tr>
<tr>
<td>Peak weight loss from birth 7% +/- 2.5% (peak on day 3)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Outcomes


Reasons for readmission:
- pertussis
- RSV
- bacteremia
- hypoglycemia
- fever
- diarrhea
- failure to thrive
- ATE with reflux
Clinical Outcomes

Methadone Treatment Variables (N=117)

- Average discharge methadone dose: 0.5 ± 0.25 mg/kg/day
- 0.6 mg every 12 hours

4-week weaning calendar; weekly PCP visits during wean
All doses dispensed to family in prefilled syringes from GMH outpatient pharmacy
Cost to family for medication: $7-15

Utilization Outcomes

Average Length of Stay for NAS Newborns

Cost Outcomes

Mean Hospital Charges per Pharmacologically Treated NAS Case

SC Data Courtesy of SC Birth Outcomes Initiative Data Committee, 2016

95% of cases were funded by SC Medicaid
Current MAiN Program Model

MAiN (Managing Abstinence in Newborns) Program Aim: To provide multidisciplinary care to mothers with newborns at risk for or diagnosed with neonatal abstinence syndrome, in order to achieve a cost-effective, family-centered experience with best potential outcomes for mothers with substance use disorders and their exposed and/or treated infants.

- Prenatal identification of maternal opioid dependence
- Interventions to minimize NOWS risk for newborn
- Care coordination of infant and mother in low-acuity nursery
- Inpatient symptom stabilization
- Early treatment to minimize complications of NOWS
- Outpatient medication wean

MAiN Program Service Map

Next Steps: Community Hospital(s) Feasibility Study

- Share and replicate MAiN Program Model
- Recruit pilot sites in Upstate SC
- Compare patient and program outcomes
- Publication of results
- Expansion
Critical Questions

What is the effect of chronic opioid exposure on the developing brain?

- Intrauterine abstinence syndrome is life-threatening to the fetus; opioid maintenance during pregnancy is recommended to prevent preterm labor, fetal seizures and death.

- Methadone exposure may cause
  - prolonged QTc on postnatal day 1-2 (Parikh 2011)
  - disrupted brain maturation (Vestal-Laborde 2014)
  - abnormal visual development (McGlone 2013)
  - neurodevelopmental delays at 18 months and 3 years (Hunt 2008)

- Buprenorphine effects have not been well-studied. Limited evidence suggests neurodevelopmental effects similar to those of methadone, though risk of withdrawal is reported to be lower.

Critical Questions

What is the effect of acute opioid withdrawal on the developing brain?

- Excessive excitatory amino acid activation results in excitotoxic damage to developing neurons. These changes promote…increased anxiety, altered pain sensitivity, stress disorders, hyperactivity/attention deficit disorder, leading to impaired social skills and patterns of self-destructive behavior.

Anand KJS, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? Biol Neonate, 2000

Critical Questions

Are negative developmental and health outcomes the result of opioid exposure, withdrawal, parenting problems associated with substance use disorders, or all of the above?

- Childhood trauma and adverse experiences can lead to a variety of negative health outcomes, included increased risk for suicide, mood disorders, and substance use disorders in adolescence and adulthood (Dube 2001).

- Mothers with substance use disorders have higher rates of comorbid conditions, including smoking, mental health issues, criminal behavior, and a history of abuse/neglect with their children.
Why Treat NAS

The goal of treatment should be to provide comfort to the mother and infant in preventing symptoms, establishing feeding and weight gain, preventing seizures, reducing unnecessary hospitalization, maximizing mother-infant interaction and minimizing the incidence of infant mortality and abnormal neurodevelopment.

Neonatal Drug Withdrawal: AAP Committee on Drugs and Committee for Fetus and Newborn. Pediatrics, 2012


Conclusions

• Critical questions about the effects of opioids and withdrawal on the childhood development remain unanswered.

• Models exploring the prevention of NAS born to opioid-dependent mothers have not been described in the literature to date. However, neonates with iatrogenic opioid dependence are routinely weaned from opioids in order to prevent withdrawal.

• Our newborns experienced early and effective symptom control and low rates of NICU transfer, safety events, and readmission, despite a relatively short length of stay.

• This model of care may be feasible for Level 1 nurseries, have widespread applicability, and may further confer social, medical, and economic benefits associated with family-centered care, parental engagement, and shorter hospital stays.

Selected Additional Reading

• Neonatal Abstinence Syndrome: How States Can Help Advance the Knowledge Base for Primary Prevention and Best Practices of Care. Association of State and Territorial Health Officials, 2014

• Management of Neonatal Opioid Withdrawal. Vermont Department of Health, 2014

• Managing Chronic Pain in Adults with or in Recovery From Substance Use Disorders. Substance Abuse and Mental Health Services Administration Treatment Improvement Protocol 54, 2012