The Prescription Opioid Epidemic and Neonatal Abstinence Syndrome - A Public Health Approach

Stephen W. Patrick, MD, MPH, MS

THA Annual Meeting

July 7, 2016
https://www.youtube.com/watch?v=2eP5EnFSG0c
(30s to 3:40)
Happel TJ. Morphinism in its relation to the sexual functions and appetite and its effects on the offspring of the users of the drug. Tr M Soc Tennessee. 1892;162–179
The quantity of opium used in the United States has largely and rapidly increased. In 1859 the amount imported was about 72,000 pounds, in 1880, 372,000 pounds, in 1890, about a half million pounds. The legitimate demands of medicine would call for an increase in quantity commensurate with the increase in population; but see the contrast:—

The difference between the legitimate demands of medicine and the actual amount used shows how much approximately is consumed by opium eaters. This fact no doubt largely accounts for the rapid increase in the number of cases of insanity, idiocy, and imbecility in the present generation.
Case V. Mrs. — used morphine for years, and at the time of the birth of her third child was consuming eight or ten grains a day. In 1884 she gave birth to a well nourished and apparently perfectly developed boy, weight seven or eight pounds. Within twenty-four hours the child began to grow restless and nervous. In the next twenty-four hours this nervousness increased, and the child frequently became cyanotic; on the third day all the symptoms grew worse, the cyanotic condition continuing almost all the time; on the fourth day the child died. Not knowing anything...
Happel T.J. Morphinism in its relation to the sexual functions and appetite and its effects on the offspring of the users of the drug. Tr M Soc Tennessee. 1892;162–179

Transactions

of the

Fifty-Ninth Annual Session

Case V. Mrs. — used morphine for years, and at the time of the birth of her third child was consuming eight or ten grains a day. In 1884 she gave birth to a well nourished and apparently perfectly developed boy, weight seven or eight pounds. Opium and whiskey, however, began to have an effect on the system. In forty-eight hours this nervousness increased, and the child became cyanotic; on the third day all the symptoms grew worse, the cyanotic condition continuing almost all the time; on the fourth day the child died. Not knowing anything

The Sixtieth Annual Session will be held in Nashville, commencing the Second Tuesday in April, 1893.
1827 Morphine marketed by Merck
- Pain relief
- Treatment of ‘opium addiction’
- Treatment of ‘alcoholism’


Additional Source: Hendree Jones, PhD
1874 Diacetylmorphine discovered

1906 American Medical Association approved Heroin for general use and recommended that it be used in place of morphine.


Additional Source: Hendree Jones, PhD
PROGNOSTIC VALUE OF IMMUNOLOGIC MARKERS IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

To the Editor: The letter from Dr. Bitran has raised an important but as yet unsettled question about prognostic factors in acute lymphoblastic leukemia in adults. On the basis of experience with 13 patients, Dr. Bitran suggested that adults with T-cell disease could have a limited survival and a lower rate of remission than those with B-cell disease. From January, 1974, to June, 1979, we studied 42 consecutive adults (more than 12 years old) with acute lymphoblastic leukemia for sheep-erythrocyte rosette formation and surface immunoglobulins. Patients were classified as having T-cell disease if they had more than 40 per cent of marrow blast cells forming E-rosettes, or B-cell disease if they were positive for surface immunoglobulins. Details on the techniques have been reported elsewhere. There were 31 patients with null-cell leukemia, eight with T-cell leukemia, and four with B-cell leukemia. All patients were treated with vincristine (1.6 mg per square meter of body-surface area each week in five to six doses), daunorubicin (40 mg per square meter in two to three doses), and prednisone (40 mg per square
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1996 • American Pain Society “Pain as the 5th Vital Sign Campaign”

1998 • Federation of State Medical Boards published "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."

2003 • The New York Times reports tripling of young adults (18-25) abusing opioid pain relievers. DEA and FDA create task force to crack down on internet sales of opioids.

2007 • Maker of OxyContin, Purdue Pharma, plead guilty to “criminal charges that they misled regulators, doctors and patients about the drug’s risk of addiction and its potential to be abused.” Results in a $600M settlement.

2000+ • Rapid expansion of opioid use in the US

Trends in Opioid Use

History

Trends in Opioid Use

Substance Exposure in Pregnancy

NAS

Federal and State Policy

@stephenwpatrick
Opioid Pain Reliever Sales

Centers for Disease Control and Prevention
Opioid Pain Reliever Deaths

Centers for Disease Control and Prevention

@stephenwpatrick
Tennessee #2 in US

Number of painkiller prescriptions per 100 people

- 52-71
- 72-82.1
- 82.2-95
- 96-143

Opioid Prescription Rates by County—TN, 2007

Source: Michael Warren, MD, MPH – Tennessee DOH

Data source: Tennessee Department of Health; Controlled Substance Monitoring Database.
Opioid Prescription Rates by County—TN, 2008

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Source: Michael Warren, MD, MPH – Tennessee DOH
Opioid Prescription Rates by County—TN, 2011

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Data source: Tennessee Department of Health; Controlled Substance Monitoring Database.
Opioid Pain Relievers

- Prescriptions grew 4-fold over last decade
- Now account for more overdose deaths than cocaine and heroin combined
- More deaths than car accidents
- In 2012, enough OPR were prescribed to give every adult in the US one prescription

Source: Centers for Disease Control and Prevention
Substance Exposure in Pregnancy

- History
- Trends in Opioid Use
- Substance Exposure in Pregnancy
- NAS
- Federal and State Policy
Women aged 15-44 years who filled a prescription for an opioid medication, 2008-2012

What about Other Drugs?

• Illicit drug use in pregnancy (averaged across 2011-2012)
  – 18.3% - pregnant girls 15 to 17 years old
  – 9.0% - pregnant women 18 to 25 years old
  – 5.9% - 15-44 years (less than non-pregnant 10.7%)

• Legal drugs in pregnancy
  – 17.6% smoke cigarettes
  – 9.4% use alcohol

What about Other Drugs?

• 440,000 infants exposed to illicit drugs and alcohol per year
  – Only 5% detected at birth

What is NAS?

• A withdrawal syndrome experienced by drug exposed newborns after birth
• Generally follows opioid exposure, though other drugs have been implicated
  – Alcohol, benzodiazepines (valium, etc.), barbiturates (phenobarbital, etc.)
• 40-80% of heroin and methadone exposed newborns develop NAS
  – 7% of those exposed to opioid pain relievers?
Clinical Features of NAS

- **GI**
  - Poor feeding/vomiting/loose stools
    - Leading to dehydration and poor weight gain
- **CNS**
  - Tremors/hypertonia
  - Irritability/decreased sleep
  - Exaggerated reflexes (e.g. moro)
  - Seizures
- **Autonomic activation**
  - Tachypnea
  - Yawning
  - Dilated pupils
Making the Diagnosis

• Not every exposed newborn has withdrawal
• Exposure: history, maternal drug screens (urine), infant drug screens (urine, umbilical cord, meconium)
• Diagnosis made based on scoring system of newborn signs of withdrawal
<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGN</th>
<th>SCORE</th>
<th>Gastrointestinal disturbances</th>
<th>Respiratory/vasomotor disturbances</th>
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<td>Central nervous system</td>
<td>High pitch/excessive cry</td>
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<td>Excessive sucking</td>
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<td></td>
<td>Continuous (high pitched) cry</td>
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<td>Poor feeding*</td>
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<td>Sleeps less than 1 hour after feeds</td>
<td>3</td>
<td>Regurgitation*</td>
<td>2</td>
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<td>Sleeps less than 2 hours after feeds</td>
<td>2</td>
<td>Projectile vomiting</td>
<td>3</td>
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<tr>
<td></td>
<td>Sleeps less than 3 hours after feeds</td>
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<td>Loose stools</td>
<td>2</td>
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<tr>
<td></td>
<td>Hyperactive Moro reflex</td>
<td>2</td>
<td>Watery stools</td>
<td>3</td>
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<tr>
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<td>Markedly hyperactive Moro reflex</td>
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<td>Sweating</td>
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<td>Mild tremors disturbed*</td>
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<td>Fever 37.3 to 38.3°C</td>
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<td>Mod/severe tremors disturbed*</td>
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<td>Fever 38.4°C and above</td>
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<tr>
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<td>Mild tremors undisturbed*</td>
<td>3</td>
<td>Frequent yawning (&gt; 3 – 4 in ½ hr)</td>
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<td>Mod/severe tremors undisturbed*</td>
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<td>Mottling</td>
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<td>Increased muscle tone</td>
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<td>Nasal stuffiness</td>
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<td>Excoriation*</td>
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<td>Sneezing (&gt; 3 – 4 in ½ hr)</td>
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<td></td>
<td>Myoclonic jerks</td>
<td>3</td>
<td>Nasal flaring</td>
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<td></td>
<td>Generalised convulsions</td>
<td>5</td>
<td>Respiratory rate &gt; 60/min</td>
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<td>Respiratory rate &gt; 60/min and retractions</td>
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NAS Scoring Issues

• Scoring Tools
  – Have not undergone rigorous instrument development
  – Significant inter-rater reliability challenges

• Scoring Cut-point Threshold

• Scoring Context
  – Never tested in preterm infants
  – Tested on pure opiate-exposed population
  – Currently poly-substance exposure is the norm
  – Finnegan paper = average LOS was 6 days . . .

Source: Madge Buss-Frank
@stephenwpatrick
NAS Treatment

• Goal of treatment to “control” withdrawal, minimizing complications (e.g. seizure)
• Non-pharmacologic intervention (e.g. environmental controls, etc)
• Involves using opioids (morphine, methadone) and slowing decreasing dose
More Opioids = More NAS?
Incidence of NAS in the US, 2000-2012


@stephenwpatrick
Mean LOS and Hospital Charges for NAS, 2009-2012

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<td>Mean LOS (day)</td>
<td>22.7</td>
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<td>Mean Charges* (2012 US$)</td>
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*p<0.001

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<td>$75,700</td>
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<td>$87,700</td>
<td>$93,400</td>
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Proportion of NICU Days, By NICU (N=299)


@stephenwpatrick
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<td>$560M</td>
<td>$870M</td>
<td>$900M</td>
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<td>Private Payer*</td>
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<td>Other Payer*</td>
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<td>Total Charges*</td>
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## Total Hospital Charges for NAS, 2009-2012

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<td>Other Payer*</td>
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<td>$30M</td>
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<td>Total Charges*</td>
<td>$730M</td>
<td>$1.1B</td>
<td>$1.2B</td>
<td>$1.5B</td>
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NAS in Tennessee

NAS Risk

- Prescription opioids include
  - Short-acting (e.g. hydrocodone)
  - Long-acting (e.g. oxymorphone ER)
  - Maintenance (e.g. methadone, buprenorphine)

- Factors associated with developing NAS unclear
  - Dose (only evaluated for maintenance drugs)
  - Tobacco
  - Selective Serotonin Reuptake Inhibitor
### Characteristics of Mothers

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<td><strong>N</strong></td>
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#### Maternal race
- African American
- Caucasian
- Other

#### Psychiatric Diagnoses
- Depression
- Anxiety

#### Other Exposures
- Tobacco
- SSRI (at delivery)
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**Other Exposures**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No Opioid</th>
<th>Any Opioid Use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>25.8%</td>
<td>41.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SSRI (at delivery)</td>
<td>1.9%</td>
<td>4.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
*Results shown after adjustment for maternal age, education, race, infant gender, birthweight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure (p<0.001), drug type and number of cigarettes smoked per day.
Implications

• Medicaid insures ~80% of infants with NAS
  – States well-positioned to minimize unnecessary opioid use in pregnancy
• The AAP recommends observation of opioid exposed infants for 4-7 days
  – Low-risk discharged sooner?
  – High-risk closer observation?
NAS Care Improvement
NAS Treatment

• No clear optimal treatment
• Opioid (e.g. morphine or methadone) for opioid withdrawal
• American Academy of Pediatrics 2012 Policy statement
  – Every hospital should have a protocol
    • Adhering to protocols improves outcomes
  – Data suggests this is not occurring

NAS Quality Collaborative

• Vermont Oxford Network
  – >1000 NICUs around the world engaged in quality improvement
• In 2012, 199 centers enrolled in a NAS focused improvement collaborative
  – Toolkit focused on understanding process
  – Interactive webinar
  – Digital communication
  – Real time center-specific feedback
# Infant Outcomes

<table>
<thead>
<tr>
<th></th>
<th>February 2013</th>
<th>August 2013</th>
<th>February 2014</th>
<th>August 2014</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of treatment</strong></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.008</td>
</tr>
<tr>
<td>(days)</td>
<td>16 (10, 27)</td>
<td>15 (10, 23)</td>
<td>15 (10, 24)</td>
<td>15 (10, 24)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(days)</td>
<td></td>
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N=3,458

Patrick SW, Schumacher RE, Horbar JD, Buus-Frank M, et. al., Improving Care for Infants with Neonatal Abstinence Syndrome: A Multicenter Prospective Collaborative.
## Infant Outcomes

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<th>August 2014</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>16 (10, 27)</td>
<td>15 (10, 23)</td>
<td>15 (10, 24)</td>
<td>15 (10, 24)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>(days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong></td>
<td>21 (14, 33)</td>
<td>20 (14, 28)</td>
<td>20 (14, 29)</td>
<td>19 (15, 28)</td>
<td>&lt;0.001</td>
</tr>
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</tbody>
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Collaborative Summary

- Decreased LOT, LOS
  - Proportion of infants discharged home on pharmacotherapy decreased
- In adjusted analyses, scoring standardization associated with lowest LOT/LOS
- Centers focusing on keeping mom/baby together
- Estimated savings of 2 day shorter hospital stay: $170M
EPIDEMIC: RESPONDING TO AMERICA’S PRESCRIPTION DRUG ABUSE CRISIS
White House Plan

• **Education**
  – Parents, youth, and patients
  – Requiring prescribers to receive education on the appropriate and safe use, and proper storage and disposal of prescription drugs

• **Monitoring**
  – Every state with a Prescription Drug Monitoring Program
  – Work towards interstate interoperability
White House Plan

• Proper Medication Disposal
  – Develop convenient and environmentally responsible prescription drug disposal programs to help decrease the supply of unused prescription drugs in the home.

• Enforcement
  – Provide law enforcement with the tools necessary to eliminate improper prescribing practices and stop pill mills.
NAS Policy
PRENATAL DRUG USE AND NEWBORN HEALTH

Federal Efforts Need Better Planning and Coordination
GAO: Highlights

• NIH Funding from 2008-2013
  – $21.6 million

• 14 federal programs provide direct services

• Need coordination, suggest one HHS contact
  – “there is a risk that federal efforts may be duplicated, overlapping, or fragmented”
Rep Clark, Sen McConnell, Sen Casey, Rep Stivers introduce bill to help newborns suffering from opiate dependency
Protecting Our Infants

**HHS:**
- Review and improve coordination in HHS
- Develop a strategy to address gaps in federal policy
- Study and develop recommendations for preventing and treating prenatal opioid use and NAS
- Improve data and public health response by providing support to states and tribes

Signed by President 11/25/15
Tennessee: Criminal Justice vs. Public Health

• **Safe Harbor Act of 2013**
  – “ensure that family-oriented drug abuse or drug dependence treatment is available”
  – Treatment by 20\(^{th}\) week -> No prosecution, no child removal just for history of drug misuse

• **Public Chapter 820**
  – A woman can be charged with a misdemeanor if she illegally uses narcotics during pregnancy and if the baby is harmed as a result (ex. Neonatal Abstinence Syndrome)
Moving forward …
Care in the US for NAS

• Financial incentives are misaligned
  – Hospitals/providers are still paid to treat and to provide care
  – No incentive to decrease variable care
  – No incentive to ensure safe transition home
  – No incentive to break silos

• Dyad often separated

• Population health effects evident
Health of a Population

Experience of Care

Per Capita Cost

The Triple Aim
A Triple Aim Improvement and Research Agenda

• Experience of Care
  – Family centered care
  – Keep dyad together

• Health of the population
  – Minimize opioid complications (e.g. NAS, OD death)

• Reduce per capita cost
  – Minimize unnecessary Rx
  – Reduce variability -> decrease LOS
Targets

Birth

- Public health systems to prevent opioid dependency
  - Prescription drug monitoring programs
  - Access to treatment
- Decreasing proportion of unplanned pregnancies among opioid dependent women (~90%)
Targets

- Identification of substance use disorders in pregnancy
- Decrease overprescribing in pregnancy
- Evaluating co-morbidities in pregnancy (e.g. infectious, psychiatric)
- Identify targets to reduce risk (harm reduction) for mother and infant
Targets

• Improve identification of at risk infants
• Decrease transfers to tertiary care facilities, improve and sustain treatment in the community
• Improve care standardization and decrease variability
Targets

Birth

| Pre-Pregnancy | Prenatal | Neonatal | Childhood & Beyond |

• Decrease readmission risk
• Understand long-term risks
• Find modifiable risks (e.g. long medication tapers and risk of developmental delay)
Challenges Remain

• What does quality care for NAS look like?
  – Hospital level
  – Population/health plan

• How might alternative payment models play a role?

• How might public payers play a role (i.e. Medicaid)?
Conclusions

• Opioid misuse is not new
• Recent rise of opioid use and NAS left the health system unprepared
• Public health approaches are needed
• Care for NAS needs standardization
  – Better identification
  – Site of care
  – More efficient care
• Improving care focusing on “Triple Aim” and the continuum of care
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Thank you!

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What is NAS?

• A withdrawal syndrome experienced by drug exposed newborns after birth
• Generally follows opioid exposure, though other drugs have been implicated
  – methadone > buprenorphine > long-acting opioids > short-acting opioids
<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGN</th>
<th>SCORE</th>
<th>Gastrointestinal disturbances</th>
<th>Respiratory/vasomotor disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High pitch/excessive cry</td>
<td>2</td>
<td>Excessive sucking</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Continuous (high pitched) cry</td>
<td>3</td>
<td>Poor feeding*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleeps less than 1 hour after feeds</td>
<td>3</td>
<td>Regurgitation*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleeps less than 2 hours after feeds</td>
<td>2</td>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps less than 3 hours after feeds</td>
<td>1</td>
<td>Loose stools</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hyperactive Moro reflex</td>
<td>2</td>
<td>Watery stools</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Markedly hyperactive Moro reflex</td>
<td>3</td>
<td>Sweating</td>
<td>1</td>
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<tr>
<td></td>
<td>Mild tremors disturbed*</td>
<td>1</td>
<td>Fever 37.3 to 38.3°C</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mod/severe tremors disturbed*</td>
<td>2</td>
<td>Fever 38.4°C and above</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild tremors undisturbed*</td>
<td>3</td>
<td>Frequent yawning (&gt; 3 – 4 in ½ hr)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mod/severe tremors undisturbed*</td>
<td>4</td>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Increased muscle tone</td>
<td>2</td>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Excoriation*</td>
<td>1</td>
<td>Sneezing (&gt; 3 – 4 in ½ hr)</td>
<td>2</td>
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<tr>
<td></td>
<td>Myoclonic jerks</td>
<td>3</td>
<td>Nasal flaring</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Generalised convulsions</td>
<td>5</td>
<td>Respiratory rate &gt; 60/min</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory rate &gt; 60/min and retractions</td>
<td>2</td>
</tr>
</tbody>
</table>

NAS Scoring Issues

• Scoring Tools
  – Have not undergone rigorous instrument development
  – Significant inter-rater reliability challenges

• Scoring Cut-point Threshold

• Scoring Context
  – Never tested in preterm infants
  – Tested on pure opiate-exposed population
  – Finnegian paper = average LOS was 6 days . . .
  – Currently poly-substance exposure is the norm

Source: Madge Buus-Frank
NAS Treatment

• Goal of treatment to “control” withdrawal, minimizing complications (e.g. seizure)
• Non-pharmacologic care
• Involves using opioids (morphine, methadone) and slowing decreasing dose
Hospital Policies

Maternal substance use screen
- Evaluation and treatment
- Standardization scoring
- Non-pharmacologic treatment
- Pharmacologic treatment
- Breastfeeding

Michael D. Warren, MD¹, Angela M. Miller, PhD¹, Julie Traylor, MPH¹, Audrey Bauer, DVM¹, Stephen W. Patrick, MD² (Author affiliations at end of text)

• First state to begin public reporting
• Able to target prevention efforts
• Several other states following suit
  – Kentucky, Ohio, Massachusetts, Indiana
Neonatal Abstinence Syndrome, Tennessee, 2013