Second Annual Neonatal Scientific Workshop at the EMA

Welcome

September 12\textsuperscript{th} – 13\textsuperscript{th}, 2016
Agenda – September 12th, Afternoon

1:00 - 2:15 p.m.  **Session II: INC Workgroup Updates**
RON PORTMAN, INC CO-DIRECTOR (NOVARTIS)

2:15 – 3:00 p.m.  **Session III: Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome**
JOHN VAN DEN ANKER (CHILDREN’S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN’S HOSPITAL) & JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS

3:00 - 3:30 p.m.  **COFFEE BREAK**

3:30 – 5:00 p.m.  **Session III Panel**

5:00 p.m.  **Concluding Remarks for Day 1**
JON DAVIS (TUFTS UNIVERSITY), INC CO-DIRECTOR

6:30 p.m.  **NETWORKING DINNER AT THE PEARSON ROOM**
16-19 Canada Square, Canary Wharf
Session III: Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome

JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN’S HOSPITAL) &
JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS

The Opioid Epidemic and Neonatal Abstinence Syndrome
STEPHEN PATRICK (VANDERBILT UNIVERSITY)

The Use of Narcotics for Sedation or Analgesia
JACOB ARANDA (UNIVERSITY HOSPITAL – BROOKLYN)

3:00 – 3:30 p.m. COFFEE BREAK

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3:00 – 3:30 p.m. COFFEE BREAK

3:30 – 5:00 p.m. SESSION III PANEL
Prescription Opioid Use in Pregnancy and Neonatal Abstinence Syndrome

Stephen W. Patrick, MD, MPH, MS
Vanderbilt University School of Medicine
International Neonatal Consortium
September 12, 2016
Trends in Opioid Use

NAS

Research Gaps
ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients, Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

Jane Porter
Hershel Jick, M.D.
Boston Collaborative Drug Surveillance Program
Waltham, MA 02154


ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

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Boston University Medical Center
Waltham, MA 02154


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 → NAS → Research Gaps
United States, 1999–2010

Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w
Rates of Opioid Pain Reliever (OPR) Overdose Death, OPR Treatment Admissions, and Kilograms of OPR Sold

United States, 1999–2010

Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

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http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w
Some states have more painkiller prescriptions per person than others.

Opioid Pain Relievers in the US

• 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
• Heroin use and overdoses increasing

Source: Centers for Disease Control and Prevention
Global Opioid Consumption Morphine Equivalence (ME) (mg/capita)

Sources: International Narcotics Control Board; World Health Organization population data
By: Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center, 2015
History

Trends in Opioid Use

NAS

Research Gaps
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
  • ~5% 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>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system disturbances</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>
</tr>
<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>
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<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 rejections</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
  • Currently poly-substance exposure is the norm
  • Finnegan paper = average LOS was 6 days . . .

Source: Madge Buus-Frank
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 weaning dose


NAS in 28 US States, 2013

Incidence rates per 1000 hospital births

## Mean LOS and Hospital Charges for NAS, 2009-2012

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean LOS (day)</strong></td>
<td>22.7</td>
<td>22.9</td>
<td>22.8</td>
<td>23.0</td>
</tr>
<tr>
<td><strong>Mean Charges</strong></td>
<td>$75,700</td>
<td>$80,500</td>
<td>$87,700</td>
<td>$93,400</td>
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<tr>
<td><em>(2012 US$)</em></td>
<td></td>
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</tbody>
</table>

*p<0.001

Proportion of NICU Days, By NICU (N=299)

## Total Hospital Charges for NAS, 2009-2012

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicaid*</td>
<td>$560M</td>
<td>$870M</td>
<td>$900M</td>
<td>$1.2B</td>
</tr>
<tr>
<td>Private Payer*</td>
<td>$130M</td>
<td>$170M</td>
<td>$210M</td>
<td>$200M</td>
</tr>
<tr>
<td>Self Pay*</td>
<td>$20M</td>
<td>$40M</td>
<td>$30M</td>
<td>$40M</td>
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<tr>
<td>Other Payer*</td>
<td>$14M</td>
<td>$30M</td>
<td>$30M</td>
<td>$30M</td>
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<tr>
<td>Total charges*</td>
<td>$730M</td>
<td>$1.1B</td>
<td>$1.2B</td>
<td>$1.5B</td>
</tr>
</tbody>
</table>

* p<0.001

Research Gaps

History → Trends in Opioid Use → NAS → Research Gaps
Where are the intervention points? How can we improve research and data?
PRENATAL DRUG USE AND NEWBORN HEALTH

Federal Efforts Need Better Planning and Coordination
<table>
<thead>
<tr>
<th>Research gap</th>
<th>Number that cited gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of prenatal opioid use, including medication-assisted treatment</td>
<td>13</td>
</tr>
<tr>
<td>Long-term effects of prenatal opioid exposure in children</td>
<td>12</td>
</tr>
<tr>
<td>Treatment of NAS</td>
<td>11</td>
</tr>
<tr>
<td>Screening and diagnosing of NAS</td>
<td>10</td>
</tr>
<tr>
<td>Understanding of NAS and severity of NAS</td>
<td>10</td>
</tr>
<tr>
<td>Appropriate research methods or available data (i.e., studies of appropriate size and applied research)</td>
<td>7</td>
</tr>
<tr>
<td>Knowledge of best practices in opioid prescribing</td>
<td>5</td>
</tr>
<tr>
<td>Prevention, including prevention of substance use disorders or pregnancy in women with opioid use disorders</td>
<td>4</td>
</tr>
<tr>
<td>Screening for prenatal opioid use</td>
<td>2</td>
</tr>
<tr>
<td>Understanding prenatal opioid use</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: GAO. | GAO-15-203
GAO Noted Research Gaps

• Specifics noted –
  • Treatment of opioid use disorders in pregnant women – universal screening?
    • Best practices for MAT; barriers to treatment
  • Subjectivity and labor intensiveness of Finnegan NAS Tool
  • Treatment of NAS
  • Effectiveness of different drugs
  • Long-term outcomes of opioid-exposed infants
• Barriers to research
  • Identifying and retaining pregnant women
    • Low numbers; high drop out rates
    • Reluctance to participate due to possible criminal repercussions
  • Polysubstance use
  • Variation in expression of NAS
  • Need for large numbers
  • Funding
  • Capacity (multidisciplinary teams needed)
What is needed?

• Standardization/structure for international research efforts
• What is NAS/NOWS?
  • Gold standard definition
  • Objective means for diagnosis, validated
• Relevant outcomes
  • Not limited to utilization (e.g. length of stay, not family centered, does not take post-discharge outcomes into account)
  • Standardized outcomes for site/international comparisons
Summary

• Opioid use and NAS are not new, but challenges with recent surges
• Opioid use and NAS are international problems, with particularly high rates in North American, Europe and Australia
• A coordinated, international agenda will facilitate better research and more effective coordination ultimately improving outcomes for this vulnerable population
Acknowledgements

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Thank you!

stephen.patrick@vanderbilt.edu
Prescribing and NAS

- Study from our group - >110,000 TN births
  - >31,000 women prescribed opioids (96% short-acting)
  - More likely to have co-occurring psychiatric diagnoses
- 2/3 of infants with NAS, mother with legal Rx
  - Smoking increased risk of NAS
  - Higher dose of immediate release increased risk of NAS
  - Dose of maintenance drugs did not change risk
  - 1:50, Short-acting opioid cost: infant cost

Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome

2:15 – 3:00 p.m.  Session III: Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome
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3:00 – 3:30 p.m.  COFFEE BREAK

3:30 – 5:00 p.m.  SESSION III PANEL
Analgesia and Sedation in the Newborn

J.V. Aranda, MD,PhD,FRCPC,FAAP
Professor and Director of Neonatology and the U54 New York Pediatr Developmental Pharmacol Res Center State University of New York Downstate Medical Center Brooklyn, New York, NY
Email: jaranda@downstate.edu
Scope

1. Use of analgesics and sedation in NICUs
2. Outcome of unrelieved pain and treatments
3. Pain assessment and quantification in Newborns
4. Opiates
5. Sedatives
6. NSAIDs
7. GAPs in knowledge: Pharmacotherapy of Pain and Stress in newborns
8. Questions and Comments along the way
Basic Principles - Neonatal Pain

• Newborns can feel pain
• Humane and Ethical IMPERATIVE to provide comfort and relieve pain in a vulnerable, non-verbal population
• Increased pain sensitivity due to immature pain modulatory mechanisms
• Prolonged hyperalgesia following tissue injury
• Acute physiologic and behavioral responses to painful stimuli
Analgesia and Sedation Practices in NICUs

Wide variation occur in NICU’s and Countries

Pain control

Known and unknown
Acute and long term
Adverse effects
Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study


Oct 2012–June 2013, 234 NICUs, 18 countries
Prospective Cohort
N=6680
Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study


<table>
<thead>
<tr>
<th>Country</th>
<th>Bolus only</th>
<th>Continuous only</th>
<th>Continuous and bolus</th>
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</thead>
<tbody>
<tr>
<td>Total (n=2142)</td>
<td>46.7%</td>
<td>13.7%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Austria (n=22)</td>
<td>45.5%</td>
<td>46.0%</td>
<td>8.5%</td>
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<tr>
<td>Belgium (n=37)</td>
<td>8.1%</td>
<td>46.0%</td>
<td>48.0%</td>
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<tr>
<td>Cyprus (n=41)</td>
<td>97.6%</td>
<td>58.8%</td>
<td>38.8%</td>
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<tr>
<td>Estonia (n=17)</td>
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<td>58.8%</td>
<td>10.0%</td>
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<tr>
<td>Finland (n=52)</td>
<td>42.3%</td>
<td>58.8%</td>
<td>10.0%</td>
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<td>France (n=497)</td>
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<td>Germany (n=29)</td>
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<td>24.6%</td>
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<td>89.5%</td>
<td>24.6%</td>
<td>7.9%</td>
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<tr>
<td>UK (n=713)</td>
<td>83.0%</td>
<td>24.6%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

*Data from the EUROPAIN Survey Working Group.
### Tracheal Intubation-ventilation

![Graph showing percentages of drugs used in tracheal intubation-ventilation.

### Non-Invasive ventilation

![Graph showing percentages of drugs used in non-invasive ventilation.

#### Other Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total (n=2064)</th>
<th>Tracheal Vent (n=1139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>326 (16%)</td>
<td>229 (20%)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>15 (1%)</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>Local anesthetics</td>
<td>8 (&lt;1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Nueromuscular blockers</td>
<td>259 (13%)</td>
<td>259 (23%)</td>
</tr>
<tr>
<td>Pain scale use</td>
<td>1136 (55%)</td>
<td>682 (60%)</td>
</tr>
<tr>
<td>Withdrawal syndrome</td>
<td>15 (1%)</td>
<td>13 (1%)</td>
</tr>
</tbody>
</table>
Questions-Comments

• Establish Priority

• Which drug should we study first and why?

• If your decision is already made up, what, how and why did you choose the drug?
Increasing opiate use and increased iatrogenic withdrawal in NICU

**Lewis et al: J Opioid Manag 2015: 11:305-312**

### Drug exposure

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Continuous opiate infusion</td>
<td>15.2 (27.3)</td>
<td>17.0 (13.8)</td>
<td>21.6 (22.3)</td>
<td>0.094</td>
</tr>
<tr>
<td>Days -paralytics</td>
<td>1.5 (2.1)</td>
<td>1.8 (5.0)</td>
<td>3.4 (4.7)</td>
<td>0.434</td>
</tr>
<tr>
<td>Days-benzodiazepine</td>
<td>13.3 (34.8)</td>
<td>15.4 (17.2)</td>
<td>18.8 (25.5)</td>
<td>0.305</td>
</tr>
<tr>
<td>Required weaning-N(%)</td>
<td>11 (53%)</td>
<td>10 (71%)</td>
<td>23 (82%)</td>
<td>0.068</td>
</tr>
<tr>
<td>Discharge Dx-NAS: N(%)</td>
<td>2 (9%)</td>
<td>5 (36%)</td>
<td>14 (50%)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

### Opiate: Morphine: Opiate Equivalence ratio

- Morphine: 1:1 (IV or po)
- Fentanyl: 20:1 (IV)
- Hydromorphone: 5:1 (IV)
- Methadone: 10:1 (IV and po)
- DTO (Diluted tincture of Opium): 0.4:1 (always po)
NICU Iatrogenic withdrawal

• 15/30 newborn survivors treated for CDH with ECMO (2003 to 2005)
• 5/15 weaned at home (telephone contact once a week.)
• Weaning at home took 11, 42, 107, 173, and 180 days.

How soon do addiction and tolerance develop in newborns?

- Tolerance and withdrawal noted after 3 days of opiate therapy
- Fentanyl dose doubles within 5 days in ECMO babies to obtain similar pharmacologic effect
QUESTION

• Would alternating Opiates with other analgesics eg NSAIDs, propofol etc decrease risk of addiction or tolerance ??
Pharmacologic Control of Pain in Newborn

1. NSAIDS: Paracetamol, ibuprofen, Ketorolac
2. Sedatives: Benzodiazepines, Midazolam, Diazepam
3. Opiates: Morphine, Fentanyl, Sufentanil, codeine, Alfentanil, Remifentanil
4. Recent: ketamine, propofol, dexmedetomidine
5. Local Anesthetics - EMLA, Lidocaine, Prilocaine
6. Sucrose
Pain in Newborns – Assessment
Outcome tools for analgesia studies

- > 40 Pain Scores: (multidimensional: physiologic, behavioral)
- Commonly used Scoring tools (validated for gest. Age)
  4. Behavioral Infant Pain Profile - BIPP (Holsti Pain 2007)
  5. Doleur Aiguë du Nouveau-né-DAN (Carbajal Arch Pediatr 1997)
Pain in newborns “surrogate biomarkers” for analgesia evaluation

- Near infra-red spectroscopy
- Amplitude integrated EEG
- Functional MRI
- Heart rate variability
- Skin conductance
- Skin blood flow
- Crying – spectrographic and power spectrum
- Biochemical/hormonal – catecholamines, cortisol, glucagon, beta-endorphins
Morphine

• Preferred use in ventilated newborns in part due to respiratory depressant effect


Acute Adverse effects: Hypotension, Seizures, Histamine release -- Bronchospasm
Metabolic pathway of morphine and codeine

http://www.pharmgkb.org/search/pathway/codeine-morphine/codeineMorphine-pk.jsp#

accessed Feb 19, 2012
Morphine

- Pop PK derived non-linear morphine Loading dose: 100 microgm/kg; maintenance dose of 5 μg/kg^{1.5}/h, with a 50% dose reduction in neonates with a postnatal age (PNA) <10 days (Krekels 2014)

- Polymorphisms: OPRM1 118A>G (asn^{40}asp), COMT 472G>A (val^{158}met) and ARRB2 8622C>T and OPRM1/COMT – increased rescue morphine doses

- UGT2B7 polymorphisms alters morphine PK (Matic, Pharmacogenomics 2014)
PHARMACOGENOMICS SHOULD BE A COMPULSARY COMPONENT OF ANY DRUG DEVELOPMENT STUDY

WHAT ARE THE RELATIVE CONTRIBUTIONS OF GENOMICS, PK/PD, METABOLISM, DISEASE STATE AND CULTURAL AND DEMOGRAPHIC FACTORS IN THE FINAL OBSERVED DRUG RESPONSE???

RECEPTOR SENSITIVITY?
## Morphine in mechanical ventilation > 7 Neonatal Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>NEOPAIN (Anand 2004)</th>
<th>Dutch Trial (Simon 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Double Blind RCT</td>
<td>Double Blind RCT</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>898</td>
<td>150</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>23-32 weeks</td>
<td>25-32 weeks</td>
</tr>
<tr>
<td><strong>Morphine Dose (mcg)</strong></td>
<td>100 mcg/kg +10 -30 mcg/kg/hr</td>
<td>100 mcg + 10 mcg/kg/hr</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Morphine in Ventilated Preterm Neonates

• Primary Outcomes from the NEOPAIN Trial (Composite of neonatal death, severe IVH or PVL)
• Anand KJS et al - Lancet 363: 1673-1682, May 22, 2004
• 898 newborns; (23-26 wks, 27-29, 30-32 wks)
• 12 US centers, 4 Euro centers
Data summary:

- No difference in primary outcomes (25.7% vs 27.4%) neonatal deaths (10.5% vs 12.9%); severe IVH (10.7% vs 13.4%) or PVL (9.3% vs 7.4%)

- Morphine: decreased pain scores (p=.002) HR(p=0.004) RR(p<0.045) but

- Increased hypotension (p<0.01) prolonged vent (p(0.034), feeding intolerance (p=0.045)
Morphine in mechanically ventilated newborns (Anand Lancet 2004)

- **Open label morphine:**
  Morphine group 202/449 (45.3%)
  Placebo group 240/449 (54.2%, p<0.008)

  **Open label morphine:**
  primary outcomes (23.6% vs 14.0%); p=.03
  severe IVH (16.2% vs 4.3% p=0.04)

- **Within Placebo group:**
  Open label morphine:
  primary outcome (34.5% vs 14.9%);
  death (13.8 vs 6.9% p=0.02)
  severe IVH (17.2% vs 3.1% p<0.001) PVL (13.2% vs 4.8% p=0.006)
Long Term Outcome: Morphine

- **Five year**: Dutch Cohort:
  Lower IQ in morphine group n=49: 94±14.5 vs 100±12.9 placebo, n=41, Visual analysis IQ subtest negatively (p<0.05) to morphine exposure. (deGraaf J, et al. Pain. 2011 Jun;152(6):13)

  - Neurological exam normal in 29 (76%) morphine and in 25 (61%) control p=0.14 (NS); No difference in Head Circumference
  - IQ: placebo: 101(SD 18) vs 99(19) morphine; p=0.63 (NS)
  - Quantitative sensory testing (QST)- no difference between groups
  - Fewer problems with daily executive functions (eg: organizing ) in morphine p<0.04
Long term outcome - Morphine

Royal Melbourne Study (Steinhorn R et al, J Pediatr. 2015 May;166:1200-1207.)

233 prems < 30 weeks gest; 57 had morphine; 176 no morphine:

- At term: MRI Morphine group had cortical gray matter with smaller orbitofrontal (p<0.002, p<0.01) and subgenual (p<0.01, p<0.02) volumes bilaterally. Had decreased tone (p=0.01)
- At 2 years: BSID-II Cognitive (MDI), motor(PDI) speech: no difference; but morphine group had more behavioral dysregulation (p<0.007)
- At 7 years: MRI findings, brain volumes similar in both groups.
  - Morphine and no-morphine groups performed similarly on measures of IQ (WASI), motor function (MABC-2), executive function (BRIEF), and behavior (SDQ).
  - Morphine group: Higher scores in basic educational skills (WRAT 4)p=0.008. which persisted across subgroup tests of reading (p=0.002) and spelling (p=0.001).
Long Term Outcome-Morphine

Neopain Cohort:
Five to Seven Year: Morphine=14; Placebo=5:
Morphine group: smaller head circumference, longer response latencies, more social problems

### Examples of Mechanisms in Neuronal damage or protection

**VEGF Signaling Genes at P14**

(Values are fold change from RA saline control)

<table>
<thead>
<tr>
<th>Genes of Interest</th>
<th>Keto/Sal RA</th>
<th>Sal/Caff RA</th>
<th>Keto/Sal O₂</th>
<th>Sal/Sal O₂</th>
<th>Keto/Sal O₂</th>
<th>Sal/Caff O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF A</td>
<td>1.7±0.03</td>
<td>1.4±0.09</td>
<td>1.2±0.47</td>
<td>2.1±0.07</td>
<td>-1.0±0.99</td>
<td>1.5±0.12</td>
</tr>
<tr>
<td>VEGFR-1</td>
<td>1.4±0.17</td>
<td>2.1±0.01</td>
<td>-1.2±0.99</td>
<td>2.3±0.07</td>
<td>-1.0±0.99</td>
<td>-1.4±0.45</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>-1.6±0.24</td>
<td>-1.0±0.71</td>
<td>-2.0±0.14</td>
<td>-1.4±0.37</td>
<td>-2.5±0.1</td>
<td>-1.8±0.18</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>1.8±0.45</td>
<td>2.0±0.35</td>
<td>1.1±0.98</td>
<td>-1.4±0.43</td>
<td>1.3±0.87</td>
<td>-1.0±0.75</td>
</tr>
<tr>
<td>NP-1</td>
<td>1.4±0.13</td>
<td>1.1±0.55</td>
<td>-1.0±0.94</td>
<td>-8.6±0.09</td>
<td>-1.2±0.49</td>
<td>-1.2±0.45</td>
</tr>
<tr>
<td>NP-2</td>
<td>1.3±0.22</td>
<td>1.6±0.01</td>
<td>-1.0±0.74</td>
<td>1.2±0.4</td>
<td>-1.1±0.55</td>
<td>-1.2±0.38</td>
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<tr>
<td>HIF1α</td>
<td>1.0±0.96</td>
<td>-1.1±0.69</td>
<td>-1.5±0.21</td>
<td>1.0±0.73</td>
<td>-1.8±0.36</td>
<td>-1.0±0.92</td>
</tr>
</tbody>
</table>

Neuropilin-1 and 2 are transmembrane proteins- coreceptor tyrosine kinase for VEGF and Semaphorins ; plays versatile roles in angiogenesis, axon guidance, cell survival, migration, and invasion and repulsive axon guidance.

**VEGFR3**: lymphatic endothelial cell development, modulated by NP2, NOTCH signaling.
SEDATION IN NEWBORNS

Indication: Stress (any sources: intubation, pain – procedural, acute, post-operative, chronic)

Drugs:
- Midazolam
- Diazepam
- Lorazepam
Benzodiazepines potentiate GABAergic neurotransmission by promoting postsynaptic receptor opening (GABA-A receptor), increased conductance to chloride ions, membrane hyperpolarization and neuronal inhibition.

Pharmacologic uses: sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.

Benzodiazepines:
- Midazolam
- Diazepam
- Lorazepam

Depolarising (excitatory) in newborn. Transition to Hyperpolarizing (inhibitory) Postnatally.
GABA_A RECEPTOR DISTRIBUTION IN A NEWBORN

Newborn MICRO-PET SCANNER
WSU-NIH/PPRU(PI- Aranda)
Midazolam

Imidazobenzodiazepine: anxiolytic, sedative, muscle relaxant and anticonvulsant
Absorption 30% - oral and 50% with nasal administration.
Rapid and extensive distribution, Highly protein bound (97%).
Hepatic metabolism to active and inactive derivatives, major metabolite (1-hydroxymidazolam) has shorter t 1/2
impaired by poor hepatic perfusion. Very slow elimination via the kidneys.
   Elimination half-life variable (6-7 hours in term infants, longer in less mature infants), major metabolite (1-hydroxymidazolam) has shorter t 1/2
Rapid onset of action (<3 minutes) and peak sedative action <20 minutes after IV administration. Anticonvulsant action may be more rapid.
The IV preparation has a pH of 3.
Midazolam

Imidazobenzodiazepine: anxiolytic, sedative, muscle relaxant and anticonvulsant

Absorption 30% - oral and 50% with nasal administration.

Rapid and extensive distribution, Highly protein bound (97%)

Hepatic metabolism : CYP3A4. major metabolite (1-hydroxymidazolam) has shorter t ½

Elimination half-life variable (6-7 hours in term infants, longer in premature infants), major metabolite (1-hydroxymidazolam) has shorter t ½

Drug clearance Not affected by hypothermia unless there is decreased liver and renal function. (Welsing 2013)

Rapid onset of action (<3 minutes) and peak sedative action <20 minutes after IV administration. Anticonvulsant action may be more rapid.
IV Midazolam in newborns

IV Midazolam: 6 randomized controlled trials
• McCarver-May 1996: single bolus dose
• Kawakami 1998: anesthetic induction
• Parkinson 1997: included newborns up to 15 years of age.

Anand 1999, n=67, 24-32 weeks gestation
Arya 2001, n= 33, < 2000 grams
Jacqz-Aigrain 1994, n= 48; 32.1 + 2.8 weeks

Primary Outcome: 5-item behavioural scale
• facial expression,
• Sucking continuous motor activity,
• excitability
• response to stimulation,
• excessive flexing
• physiological measures of sedation level
  Eg: heart rate, blood pressure

Ng et al, Cochrane 2012: NO effectiveness of midazolam infusion (n=146)
NO effect on morbidities (IVH)

MIDAZOLAM CO-ADMINISTERED WITH MORPHINE
Midazolam: Adverse Effects

- Hypotension, decreased cardiac output, particularly when used with fentanyl.
- Respiratory depression and apnoea.
- Hypotonia.
- Seizures or seizure-like activity following rapid bolus administration.
- Cerebral blood flow velocities may decrease transiently after midazolam boluses, reflecting reduction in blood pressure.
138 preterms, 24-32 weeks, MRI at 32 weeks and at 40 weeks. Cognitive Scores at 18 months by Bayley III directly associated with Hippocampus volume (p=0.003) but negatively related to midazolam dose (p 0.03) 

(Duerden Ann Neurol 2016: 79:548)
Biosynthesis of prostanoids

Indomethacin
Ibuprofen
Ketorolac
PARACETAMOL (acetaminophen)
NSAIDs IN NEWBORNS

Standard of Care:
1. Closure of Patent Ductus arteriosus- Indomethacin, ibuprofen, paracetamol
2. Prevention of Intraventricular hemorrhage- Indomethacin
3. Analgesia and Opiate Sparing Effect: Paracetamol, ibuprofen
Potential indication:
4. Prevention of ROP
Paracetamol: Metabolism and Excretion

In adults:
Paracetamol: almost exclusively metabolized by liver then excreted into urine,
• paracetamol glucuronide (47–62%)
• paracetamol sulphate (25–36%)
• paracetamol (oxidized by cytochrome P450 (CYP2E1) into 3-hydroxy-paracetamol and the toxic metabolite NAPQI or N-acetyl-p-benzoquinone-imine = (8-10%)
• unchanged paracetamol in urine (1-4%)

NAPQI- conjugated by glutathione to urinary excreted non-toxic thiol metabolites (cysteine, mercapturate, methylthioparacetamol and methanesulfinylparacetamol)
Toxicity occurs if glutathione is depleted resulting in conjugation of NAPQI with hepatocellular proteins leading to centrilobular liver necrosis.

Plasma Protein Binding:
Acetaminophen: 20%;
Indomethacin: 97.8% (Ghuman J J Mol Biol 2005)
Ibuprofen: 95% (cord blood) (Aranda JV Acta Pediatr 1997)

Gaps in Knowledge and Summary

- Age-related pharmacodynamic differences that will affect dose and the impact of active metabolites on response are not quantified.
- PK/PD Data on the Periviable Preterm (23-26 weeks) not available. Dosing guidelines in this population are needed.
- Neonatal transition from stimulatory (depolarising) to inhibitory (hyperpolarizing) GABA-A receptor is not known.
- Morphine at “low doses” may produce early adverse neurodevelopmental damage which appears to resolve by 8-9 years. High dose may produce more lasting damage.
- Relative contributions of pharmacogenomics, PK/PD and demographic characteristics to individual analgesic/sedative drug responses in neonate remains unexplored.
- Of the dozen NSAID, which is the most effective and safe drug.
- Opiate sparing effects of NSAIDs
Gaps in Knowledge and Summary

CHALLENGES IN ANALGESIC DEVELOPMENT IN NEWBORNS:

1. Quantitative Measures for Pain (Severity to Match Intervention)
2. Valid Outcome measures (Which morbidities, or surrogates)
3. Studies on the Periviable Newborn: 23 to 25 weeks
4. Appropriate Duration of Long term follow up
5. Age and maturation of drug metabolism, clearances and development of rational dose guidelines
6. Linking imaging technologies and morphology to function and neurodevelopmental evaluations
7. Physiologic based PK/PD modeling
8. Pharmacogenomic studies as a requisite component of clinical drug development
9. Technologies and feasible methods of studying receptor function in newborn babies
• THANK YOU
• QUESTIONS?
Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome

2:15 – 3:00 p.m.  Session III: Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome
JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN’S HOSPITAL) &
JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS

3:00 – 3:30 p.m.  COFFEE BREAK

3:30 – 5:00 p.m.  Session III Panel:
JACOB ARANDA (U HOSPITAL – BROOKLYN)
GERRI BAER (FDA)
ANNE GREENOUGH (KING’S COLLEGE LONDON)
WALTER KRAFT (THOMAS JEFFERSON UNIVERSITY)
STEPHEN PATRICK (VANDERBILT UNIVERSITY)
MERRAN THOMSON (HILLINGDON HOSPITAL NHS TRUST, CHIESI)
ROBERT WARD (UNIVERSITY OF UTAH)
MAREK MIGDAL (PDCO)
NAS - the UK experience

Anne Greenough
Professor of Neonatology & Clinical Respiratory Physiology
King’s College London School of Medicine
How common is the problem in the UK?

- Approximately one in a thousand women in Great Britain is dependent on opiates, the majority are of child bearing age.
  Singleton Office for National Statistics 2001
- Between 250,000 and 300,000 children of problem drug abusers in the UK
  Advisory Council on the Misuse of Drugs 2003
- Anonymous screening of women attending two inner city London antenatal clinics:
  
<table>
<thead>
<tr>
<th></th>
<th>Number screened</th>
<th>One of more illicit substances</th>
<th>Opiates (inc methadone)</th>
<th>Cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1000</td>
<td>10.6%</td>
<td>1.7%</td>
<td>8.5%</td>
</tr>
<tr>
<td></td>
<td>807</td>
<td>15.6%</td>
<td>1.4%</td>
<td>14.5%</td>
</tr>
</tbody>
</table>

  Farkas et al BJOG, Sherwood EJP
Cross country comparison

• NAS rates increased from 1997 to 2011
• Rates stabilised in the 2000s in England and West Australia, but rose steeply in the USA and Ontario
• 2011 prevalence rates per 1000 live births
  - 2.7 in England and Western Australia
  - 3.6 in the USA
  - 5.1 in Ontario

Davies et al ADC 2016
Socio-clinical profile

- 168 mother-infant pairs (Swansea, Wales)
- 97.4% also smoked (52% >10/day)
- 85.4% unemployed
- 91% unmarried
- 61.3% polydrug exposure
- Methadone, heroin, cannabis and benzodiazepines
- 30% Hepatitis C positive

Goel et al Eur J Pediatr 2011
Duration of neonatal unit stay

Mean duration 22 days – on average 3 cots per day occupied
Coghlan et al Irish Medical J 1999

Length of stay - methadone 29 days and methadone + other substances 41 days
Johnson et al Addiction 2003

Reducing neonatal stay:
• Management on the postnatal ward
  Saiki et al EJ Ped 2009
• Discharge home on medication (29% of units)
  - 58% medication administered in the community
  Grady et al ADC 2009
SIDS and substance abuse

• Meta-analysis of ten studies demonstrated SIDS risk is not specific to intrauterine cocaine exposure,
• Risk of SIDS - 3-10 times higher than the general population
• 32 infants dying suddenly and unexpectedly in the first 28 days after birth
  - 12 (37.5%) methadone and/or other substance misuse
  - all had multiple risk factors for SIDS – smoking, prematurity and inappropriate sleeping place

Cohen et al Acta Paed 2015
Substance abuse and respiratory control

- Infants of substance misusing mothers (SMM) have a dampened response to hypercarbia
  - which is greater at peak age for SIDS (Ali 2016)

- Neonates have a biphasic response to hypoxia
  - infants of SMM had a greater increase and then a greater decline in minute ventilation

Ali et al ADC 2106
My perspective on UK priorities

• Better methods of diagnosing and recording all infants affected by substance misuse (ICD codes likely to detect only a proportion).

• Identifying effective treatments for those affected by polydrug exposure (currently morphine is widely used).

• Evaluation of “non neonatal unit” care

• Can the adverse effect on infant respiratory control be reduced by changes in antenatal medication?
Panel III

“Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinance Syndrome”

Merran Thomson
Challenges - new drug development in NAS

Many challenges to overcome including:
- New disease area for pharma and FDA
- Lack of evidence based practice (RCTs etc.)
- Diverse clinical practice
  - Standard of care
    - Who to treat?
    - When to treat?
    - What to treat with?
- Health and social care attitude and processes

Can a regulatory drug development be successful?
Challenges - new drug development in NAS

1. Patient population

2. Scoring tool

3. Comparator therapy

4. Primary outcome measure

5. Long term follow up

6. Different regulatory processes for inpatient and community prescribed drugs
Challenge 1 - Population

The “real world” vs “ideal study” population

- Babies with NAS are often born into families with social/psychiatric challenges
  Consent and long term follow up challenging
- Mothers’ polysubstance use
  opioids plus nicotine, alcohol, psychotropic medications etc.
- Variable access to / and practice within drug rehab programs
  Influences maternal behaviour including antenatal care etc.
- Social service / foster care
  Restrictions on trial participation and follow up between / within states

Must develop treatment for the “real world” heterogenous population → collaborative working across several agencies etc.
Finnegan Neonatal Abstinence Scoring (FNAS) Tool

- Most commonly used psychometric assessment tool
- Key decision making tool used to:
  - Diagnose NAS
  - Assess need for treatment
  - Escalate, wean and stop treatment
  - Add adjunct therapy

**BUT**

- complex, intra / inter observer variability, repeated training etc.

**Will regulators recognise this as a validated score?**
Challenge 3 – Comparator drug

What should this be?
- No regulatory approved drug
- Placebo controlled trials – unethical
  - Excipients
  - Standard of care - morphine most commonly used drug
  - Efficacy and safety

Adjunct therapy
- No regulatory approved drug
- Placebo controlled trials – unethical
  - Excipients
  - Standard of care - phenobarbital most commonly used drug
  - Efficacy and safety
Challenge 4 – Primary outcome

Should measure the efficacy of the drug

- Length of treatment

- Secondary outcome measures
  - Length of stay
  - Need for adjunct therapy
  - Safety
Challenge 5 – Long term follow up

• Comparator population
  ? NAS babies
  ? Normal controls

• 12 months / 2 years / 5 years
  ? Achievable
  ? Payment
  ? Incentives

? What to test – validated and standardised assessment
Modeling, Dose Optimization, and Clinical Endpoints in NAS

Walter Kraft, MD
(Thomas Jefferson University
Philadelphia, PA)
The past

Empirically derived dose

Variability
  • Scoring instrument
  • Consistency of scoring
  • Varied protocols

No PK data

Case series and small RCTs

Practitioner focused
Common clinical endpoints in NAS trials

- Length of treatment
- Length of hospitalization
- Use of adjunctive rescue medication
- Total dose of opioid
Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study

Jason R. Wiles, MD¹, Barbara Isemann, RPh², Tomoyuki Mizuno, PhD³, Meredith E. Tabangin, MPH⁴, Laura P. Ward, MD¹,⁵, Henry Akinbi, MD¹,⁵, and Alexander A. Vinks, PharmD, PhD¹

**Objective** To characterize the population pharmacokinetics of oral methadone in neonates requiring pharmacologic treatment of neonatal abstinence syndrome and to develop a pharmacokinetic (PK) model toward an evidence-based treatment protocol.

**Study design** Based on a methadone dosing protocol, serum concentrations of methadone and its metabolites were assessed by high performance liquid chromatography-tandem mass spectrometry from dried blood spots. Population PK analysis was performed to determine the volume of distribution and clearance of oral methadone. Methadone plasma concentration-time profiles were simulated from the deduced PK model to optimize the dosing regimen.

**Results** There was substantial interindividual variability in methadone concentrations. Blood concentrations of methadone were best described by a 1-compartment model with first-order absorption. The population mean estimates (coefficient of variation percentage) for oral clearance and volume of distribution were 8.94 (103%) L/h/70 kg and 177 (133%) L/70 kg, respectively. Optimized dosing strategies were developed based on the simulated PK profiles. We suggest a starting dose of 0.1 mg/kg per dose every 6 hours for most patients requiring pharmacological treatment of neonatal abstinence syndrome followed by an expedited weaning phase.

**Conclusions** The proposed dosing regimen may reduce the cumulative dose of opioid and shorten the length of hospitalization. Future studies should aim to validate the simulated dosing schemes with clinical data and expand our understanding of the between-patient PK variability. (*J Pediatr* 2015; 167: 368-376).

**Trial registration** ClinicalTrials.gov: NCT01754324.

<table>
<thead>
<tr>
<th>Taper step</th>
<th>Dose (mg/kg)</th>
<th>Frequency</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>1A</td>
<td>0.1</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>1B</td>
<td>0.075</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>1C</td>
<td>0.05</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>3</td>
<td>0.03</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>q6</td>
<td>x 4</td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
<td>q8</td>
<td>x 3</td>
</tr>
<tr>
<td>6</td>
<td>0.02</td>
<td>q12</td>
<td>x 4</td>
</tr>
<tr>
<td>7</td>
<td>0.01</td>
<td>q12</td>
<td>x 4</td>
</tr>
<tr>
<td>8</td>
<td>0.01</td>
<td>q24</td>
<td>x 2</td>
</tr>
</tbody>
</table>

**Table 1. Oral methadone dosing scheme**

<table>
<thead>
<tr>
<th>Time 0-48 hrs</th>
<th>AUC (ng·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>816</td>
</tr>
<tr>
<td>Mean</td>
<td>1300</td>
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</tbody>
</table>
Simulated Dosing

A

Dosing protocol

Step 1: 0.1 mg/kg  q6 x 4
Step 2: 0.075 mg/kg q12 x 2
Step 3: 0.05 mg/kg  q12 x 2
Step 4: 0.04 mg/kg  q12 x 2
Step 5: 0.03 mg/kg  q12 x 2
Step 6: 0.02 mg/kg  q12 x 2
Step 7: 0.01 mg/kg  q12 x 2
Step 8: 0.01 mg/kg  q24

AUC$_{0-24}$ (ng·h/mL)  SD

985  1020
Cohort Analysis of a Pharmacokinetic-Modeled Methadone Weaning Optimization for Neonatal Abstinence Syndrome

Eric S. Hall, PhD¹, Jareen Meinzen-Derr, PhD¹,², and Scott L. Wexelblatt, MD¹

**Objective** To evaluate neonatal abstinence syndrome (NAS) treatment outcomes achieved using an optimized methadone weaning protocol developed using pharmacokinetic (PK) modeling compared with standard methadone weaning.

**Study design** This pre-post cohort study evaluated 360 infants who completed pharmacologic treatment for NAS with methadone as inpatients at 1 of 6 nurseries in southwest Ohio between January 2012 and March 2015. Infants were initially treated with a standard methadone weaning protocol (n = 267). Beginning in July 2014, infants were treated with a revised methadone weaning protocol developed using PK modeling (n = 93). Linear mixed models were used to calculate adjusted mean primary outcomes, including total duration of methadone treatment, total administered methadone dosage, and length of inpatient hospital stay, which were compared between weaning protocols. The use of adjunctive therapy for NAS treatment was examined as a secondary outcome.

**Results** Infants who received NAS treatment with the revised protocol experienced a shorter duration of methadone treatment (13.1 vs 16.4 days; P < .001) and shorter duration of inpatient treatment (18.3 vs 21.7 days; P < .001).

### Table IV. Hospital outcomes comparing those treated with standard vs the revised methadone weaning protocol

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard methadone (n = 267)</th>
<th>Revised methadone (n = 93)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of methadone treatment, mean, (95% CI)*</td>
<td>16.4 (15.2-17.5)</td>
<td>13.1 (11.4-14.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay, mean, (95% CI)²</td>
<td>21.7 (20.4-23.0)</td>
<td>18.3 (16.2-20.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total methadone dose, mg/kg, (95% CI)³</td>
<td>0.52 (0.42-0.62)</td>
<td>0.52 (0.39-0.64)</td>
<td>.97</td>
</tr>
<tr>
<td>Received adjunct therapy</td>
<td>25.5%</td>
<td>22.6%</td>
<td>.68</td>
</tr>
</tbody>
</table>
Mechanistic Population Pharmacokinetics of Morphine in Neonates With Abstinence Syndrome After Oral Administration of Diluted Tincture of Opium

Tao Liu, BSc¹, Tamorah Lewis, MD, PhD², Estelle Gauda, MD², Jogarao Gobburu, PhD, MBA, FCP¹, and Vijay Ivaturi, MS, PhD¹

Abstract

Conducting and analyzing clinical trials in vulnerable neonates are extremely challenging. The aim of this analysis pharmacokinetics (PK) model using data collected during a randomized control trial in neonates with abstinence morphine structural PK model after intravenous (IV) administration from previously published work was used scaling method with physiological consideration was used to extrapolate a PK profile from adults to pediatric bioavailability were estimated in NAS after oral administration of diluted tincture of opium (DTO). Goodness prediction distribution error and bootstrap method were performed for model evaluation. We successfully ex to pediatrics after IV administration. The estimated first-order absorption rate constant and bioavailability were Model evaluations showed that the model can accurately and precisely describe the observed data. The population for morphine after oral administration of DTO is reasonable and acceptable; therefore, it can be used to desc The integration of the previous population PK knowledge as prior information successfully overcomes the log neonate population.
Modeled time to stabilization
### The present and future

- Model based dosing
- Standardized protocols
- PK driven model refinement
- Randomized controlled trials AND pragmatic trials
- Multi-disciplinary approach
When to start pharmacologic treatment

Non-pharmacologic
- Minimize stimuli
- Breastfeeding
- Rooming in
- Swaddling

Pharmacologic

?
NAS areas of research interest

- PK driven dosing
  - Time to stabilization
  - Therapeutic target
  - Optimizing weaning
- Improving the Finnegan
- Opioid
  - Best opioid?
  - Weight or symptom based regimens
- Adjuncts
  - Phenobarbital vs clonidine
  - When to start, when to stop?
- Operationalizing pharmacogenetics
Can We Reduce Opioid Treatment of NAS?

Robert M. Ward, MD, FAAP, FCP
Professor Emeritus, University of Utah
Family-Centered Care Reduces Treatment, Shortens Stays

- Dartmouth multidisciplinary QI PDSA (plan-do-study-act) cycle-NAS
- Rooming-in skin to skin care 24/7, family & volunteers Psychiatry educated staff in how to work with substance abuse patients
- Delayed start of pharmacotherapy for 24 to 36 hrs when effects of SSRI’s, nicotine, and long acting opioids may confound NAS scores
- Change & standardize physician interpretation of scores with less emphasis on starting/increasing treatment with scores >8
  - Less emphasis on tremors, yawning, sneezing
  - More emphasis on crying, feeding, sleeping, diarrhea, emesis, fever, weight loss
- Nurses trained to standardize modified Finnegan scoring & retested
- Begin prenatal education classes at substance abuse treatment programs in response to parent request

Family-Centered Care Reduces Treatment, Shortens Stays

- 163 newborns enrolled from 3/2012 to 3/2015 with several PDSA cycles
- NAS cores did not change throughout the study, but---
- Morphine treatment decreased from 46% to 27%; total dose decreased from 13.7 mg to 6.6 mg
- LOS decreased from 16.9 to 12.3 days for newborns requiring opioid treatment; No change for those not needing treatment (4.2-4.4 days)
- Hospital costs for newborns needing pharmacologic treatment decreased from $19,737 to $8755
- No adverse events; no increased readmissions; no readmissions for NAS

Standardized Treatment Protocols Reduce Treatment

- 6 Ohio children’s hospitals covering 20 hospitals established 6 different NAS protocols
  - 6 protocols established guidelines for NAS identification and initiation of Rx
  - 3 also had strict weaning protocols
- Not every physician followed the protocol
  - 417 treated by a protocol, 130 did not follow a protocol
- Protocol guided treatment shortened duration of opioid treatment (32.1 to 17.7 days \( p = 0.0001 \)); shortened hospital stay (32.1 to 22.7 days, \( p = 0.004 \)).
- No difference in LOS between treatment with methadone and morphine
  
  Pediatrics 2014;134:e527–e534
Clonidine to Reduce Opioid Treatment of NAS

Dependent Opioid Receptor Without Adequate Opioid

Sympathetic Nervous System (SNS) Output

Locus Ceruleus Central Transfer

α2 Receptor

Catecholamine Output Without Clonidine

Clonidine: Alpha2 presynaptic inhibitory agonist
Dependent Opioid Receptor Without Adequate Opioid

Clonidine can minimize signs of NAS while the opioid receptor reverts to normal reactivity and stops stimulating SNS output.
Ondansetron: Another Modulator of Opioid Abstinence

- Ondansetron: Serotonin (5-HT)3a receptor antagonist
- Ondansetron: blocks narcotic withdrawal in rat & man (Peltz lab-Stanford)
  - *(Pharmacogenet Genomics. 2009;19:193)*
- Ondansetron pK pregnant women and neonates:
  - *Clin Pharmacol Ther. 2015;97:167-76*
- RCT: Pregnant women from methadone maintenance program dosed in labor to reach fetal concentration to prevent NAS & continue treatment of newborns; enrolling now; blinded; no results
- NAS TREATMENT WITHOUT NARCOTICS MAY SOON BE POSSIBLE
Voting Slide – Neonatal Abstinence Syndrome

Considering both impact and feasibility, which of the following projects is your **first** choice?

1. To develop a gold standard definition of neonatal abstinence syndrome and/or neonatal opioid withdrawal syndrome based upon objective, validated tools.
2. To develop standardized outcome and process measures for NAS/NOWS to be utilized in clinical trials.
3. To understand the impact of non-pharmacologic treatment in optimizing outcomes for women and infants impacted by the opioid use disorder and NAS, including rooming in, soothing techniques and breastfeeding in addition to and independent of various pharmacotherapies for NAS.
4. To develop a gold standard treatment protocol and standardized medication of choice for severe NAS, address the variability of dosing/drugs, and include defining the safety and role of adjunctive treatments, particularly phenobarbital.
5. To understand the predictors of NAS, both genomic and pharmacologic.
6. “Walk-in Option A” (offered up by audience)
7. None of the above
Considering both impact and feasibility, which of the following projects is your second choice?

1. To develop a gold standard definition of neonatal abstinence syndrome and/or neonatal opioid withdrawal syndrome based upon objective, validated tools.
2. To develop standardized outcome and process measures for NAS/NOWS to be utilized in clinical trials.
3. To understand the impact of non-pharmacologic treatment in optimizing outcomes for women and infants impacted by the opioid use disorder and NAS, including rooming in, soothing techniques and breastfeeding in addition to and independent of various pharmacotherapies for NAS.
4. To develop a gold standard treatment protocol and standardized medication of choice for severe NAS, address the variability of dosing/drugs, and include defining the safety and role of adjunctive treatments, particularly phenobarbital.
5. To understand the predictors of NAS, both genomic and pharmacologic.
6. “Walk-in Option A” (offered up by audience)
7. None of the above
<table>
<thead>
<tr>
<th>Time</th>
<th>Session II: INC Workgroup Updates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MARK TURNER, INC CO-DIRECTOR (UNIVERSITY OF LIVERPOOL)</td>
</tr>
<tr>
<td>2:15–3:00 p.m.</td>
<td>Session III: Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome</td>
</tr>
<tr>
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<td>JOHN VAN DEN ANKER (CHILDREN’S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN’S HOSPITAL) &amp; JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS</td>
</tr>
<tr>
<td>3:00–3:30 p.m.</td>
<td>COFFEE BREAK</td>
</tr>
<tr>
<td>3:30–5:00 p.m.</td>
<td>Session III Panel</td>
</tr>
<tr>
<td>5:00 p.m.</td>
<td>Concluding Remarks for Day 1</td>
</tr>
<tr>
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<td>JON DAVIS (TUFTS UNIVERSITY), INC CO-DIRECTOR</td>
</tr>
<tr>
<td>6:30 p.m.</td>
<td>NETWORKING DINNER AT THE PEARSON ROOM</td>
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<tr>
<td></td>
<td>16-19 Canada Square, Canary Wharf</td>
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Thank you!