The International Neonatal Consortium

Lynn Hudson – Executive Director
Jonathan Davis, Ron Portman, Mark Turner – Co-Directors

May 1 – 3, 2019
Optimizing Clinical Trials for Neonatal Opioid Withdrawal Syndrome (NOWS) and Neonatal Abstinence Syndrome (NAS)

GERRI BAER and JON DAVIS – Co-Chairs

May 2, 2019
10:30 a.m. - 12:30 p.m. Optimizing Clinical Trials for Neonatal Opioid Withdrawal Syndrome (NOWS) and Neonatal Abstinence Syndrome (NAS)

GERRI BAER AND JON DAVIS, co-chairs
• Hendree Jones (U-North Carolina)
• Gioia Guerrieri (CDER/FDA)
• Ju Lee Oei (U – New South Wales)
• Thierry Lacaze (U-Calgary, Alberta)
• Merran Thomson (Chiesi consultant)
• Norma Terrin (Tufts U)
• Walter Kraft (Thomas Jefferson U)
• Victoria Kuck (Parent representative)
• Lauren Kelly (Children’s Hospital Research Institute of Manitoba)
Session Overview

Gerri Baer and Jon Davis
• Gerri Baer
  • The views presented here are personal and do not necessarily reflect the views of the FDA
  • All specific product development questions should be discussed with the relevant review division
  • I have no conflicts of interest to disclose
  • Off-label use of medications (as always) will be discussed

• Jon Davis
  • Nothing to disclose
Why Talk About Neonatal Withdrawal Again?

- In September 2016 at EMA in London, the INC met and discussed treatment of neonatal withdrawal along with sedation and analgesia – several of today’s panelists were involved.
- It was not clear that there would be enough international interest to initiate a workstream for neonatal withdrawal.

INC has brought together key stakeholders to develop terminology, master protocols, expert white papers, adverse event scales and other projects… Is now the time for NOWS?
What is NOWS? (Why the Different Terminology?)

- "Neonatal Abstinence Syndrome (NAS)" - used since 1970’s to describe neonatal withdrawal after intrauterine exposure(s)
  - ABSTAIN v. = to choose not to do or have something; to refrain deliberately and often with an effort of self-denial from an action or practice (Merriam-Webster)
- NAS may refer to withdrawal from any number of intrauterine exposures, including opioids
- Neonatal Opioid Withdrawal Syndrome (NOWS) is a subset, specific to abrupt opioid withdrawal
- Intrauterine exposures in withdrawing neonates are commonly related to >1 compound, including both prescribed and non-prescribed drugs
Recently Published Research – The Impact of Standardizing Treatment

• Unit-Based Protocols have been successful at reducing length of treatment (LOT), length of stay (LOS), adjunctive medication use
  • East Tennessee (Saunders, et al. J Perinat Neonat Nurs 2014)

• Quality Improvement Collaboratives have shown that LOT (and LOS) can be reduced by **standardizing non-pharmacologic and pharmacologic care**
  • MEDNAX National Opioid Management Collaborative
  • Ongoing projects in CA, NY, NC, MA, WV, TN...

• With standardized protocols, the **most optimistic** estimates of LOT for infants needing pharmacologic treatment hover around **13-14 days**
Recently Published Research – Buprenorphine and NAS

• Kraft, et al. NEJM 2017
  • DB/DD RCT 63 term infants with signs of NAS -- SL buprenorphine or PO morphine
  • Median treatment duration in buprenorphine vs. morphine –15 vs 28 days
  • Adjunct medication use was similar

• Hall, et al. Am J Perinatol 2018
  • Retrospective cohort of 360 neonates with NAS – SL buprenorphine or “traditional opioid”
  • Median treatment duration in buprenorphine (n=174) vs. “opioid” (n=186) – 7 vs. 10 days

  • Retrospective cohort of 201 neonates with standardized protocols in 6 hospitals in SW Ohio
  • Median treatment duration in buprenorphine (n=38) vs. methadone (n=163) – 9 vs. 14 days; adjunct medication use was similar

• Considerable variability on duration of treatment between studies
  • Sources of variability may include: study methods (RCT vs Retrospective), treatment/dosing and tapering protocols, different assessment tools, ...
Recently Published Research – Methadone vs. Morphine

- Davis, et al. JAMA Peds 2018
  - DB RCT of 117 neonates treated for NAS – PO methadone vs. PO morphine (treated based on weight and Finnegan score)
  - Primary endpoint LOS: decreased LOS by ~3 days with methadone (LOS attributable to NAS was 16 vs. 19 days)
  - LOT decreased by 2 days with methadone (adjusted for site and maternal opioid type); unadjusted was 11.5 vs 15 days
  - Methadone-treated were less likely to receive adjunct therapy (17% vs. 29%)

- Tolia, et al. J Peds 2018 – Pediatrrix CDW cohort
  - From 2011-15, 7667 eligible infants – methadone (n=1187) vs. morphine (n=6480)
  - Methadone was associated with a shorter median LOS – 18 vs. 23 days
  - Methadone-treated were less likely to receive adjunct therapy
• ESC was developed out of a quality improvement project at Yale-New Haven Children’s Hospital (2010-2016)

• Non-pharmacologic measures were standardized (low stimulation, parent engagement, breast-feeding) with parents rooming in and providing comfort measures

• Assessment: if the infant can breastfeed or take ≥1 oz from a bottle, sleep undisturbed for ≥ 1 hour, and be consoled by 10 minutes (if crying), morphine was neither started nor increased regardless of other signs
  • If infant does not meet the criteria, and non-pharmacologic measures have been maximized, morphine was initiated or increased

• If medication was needed, the guidelines allowed more rapid decreases in morphine dose (as often as 3x per day) and/or morphine given as needed
Recently Published Research – Eat, Sleep, Console (ESC)

• Grossman, et al. Pediatrics 2017 describe patients born ≥ 35 weeks and whose mothers were on methadone for at least 1 month prior to delivery; Yale’s previous NAS treatment protocols used morphine and FNASS

• Average LOS decreased from 22 days (10 d just before ESC QI began) to ~6 days

• Average percent treated with morphine decreased from 98% (73% just before ESC QI began) to 28%

• The approach was studied at Boston Medical Center (n=54 intervention group, n=85 post-intervention), with a change from morphine to methadone (Wachman, et al. J Perinatology 2018)
  • Reduced need for pharmacologic treatment after instituting ESC
  • Reduced LOS and LOT
  • “No adverse events were noted.” No seizures, no NICU admissions. One child readmitted to restart methadone during the intervention period
Recently Published Research – Neurodevelopmental, Educational, and Behavioral Outcomes

• *Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes (2018).*¹
  
  N=96 children from the MOTHER study (mothers receiving buprenorphine vs. methadone) followed to 3 years
  • Up to 36 months, children had normal **physical, cognitive, and language development**
  • There was no differential impact of maternal buprenorphine or methadone on child development
  • There was no association between severity of NAS and development

• *Neonatal Abstinence Syndrome and High School Performance (2017).*²
  
  Linked data on 2234 children from NSW with NAS compared to 4330 controls matched for GA, SES, & gender and ~600,000 other children with **national literacy and numeracy testing**
  • Average test scores were significantly worse in 3rd, 5th, and 7th grade for children who had NAS vs controls; NAS was associated with an aOR 2.5 for not meeting minimum standards
  • In children with NAS, male gender, indigenous status, and having a parent without 9th grade education increased the risk

• **Neurodevelopmental Outcomes in Infants Treated for NAS (2018)**
  - Retrospective cohort of 87 infants treated for NAS
  - Evaluated at 2 years of age with BSID-3\textsuperscript{rd} ed, in Cincinnati Children’s NICU follow-up program
  - Average cognitive, language, and motor subscales were below the mean (100) but were all >93.8
  - Strabismus was present in 8% of children

• ESC Outcomes – none published at this time
  - Not clear how ESC will compare to other standard approaches
  - ECHO study will compare ESC to standard approach in a cluster randomized study

So...What is the Optimal Treatment Approach?

• WHAT’S KNOWN:
  • Standardizing treatment protocols, including non-pharmacologic and pharmacologic therapies, helps wean infants off medication and out of the hospital sooner

• WHAT ISN’T KNOWN:
  • What is the optimal treatment approach, including when to start and escalate medication, and when and how to taper?
  • What is the optimal choice of pharmacologic therapy and dosing strategy?
  • What is the optimal setting for infants with NOWS/NAS?
  • Are long-term outcomes affected by the particular therapy chosen? Is this knowable?
  • What are the optimal assessment tools and are there easier ways to evaluate the effectiveness of treatment or the need for treatment?

• AND OF COURSE additional roadblocks in trying to figure it out...
  • Neonatal-appropriate formulations
  • Maternal poly-pharmacy
  • Feasibility of trials
  • Definition/terminology differences
Our Outstanding Lineup!
Let’s Go!

• International Experiences and Models of Care in Canada, Australia, and Europe – 15 min
• Issues in Assessment: Diagnosis, Severity, and Response to Treatment – 10 min
  • Withdrawal Symptoms that Contribute to the Decision to Treat – 5 min
• A Clinical Trialist’s Perspective on Harmonization of Trial Elements – 10 min
• Developing Core Data Elements – 5 min
• Considerations in Regulatory Review of NOWS Products – 10 min
• Parent Perspective – 10 min

• Discussion with Panelists and Attendees – 45 minutes
NAS: The Canadian Context

Thierry Lacaze-Masmonteil, Scientific Director
Maternal Infant Child Youth Research Network (MICYRN)
Professor, Department of Paediatrics, University of Calgary
Annual Incidence per 1000 live births, 2003-2014

- British Columbia: 4.0
- Alberta: 2.7
- Saskatchewan: 7
- Manitoba: 5.7
- Ontario: 6.4
- New Brunswick: 9.7
- Nova Scotia: 7.4
- Canada (except QC): 5.4

Filteau J et al, *Drug and Alcohol Dependence* 2018; 185:313-21
Total and mean per patient hospital cost, initial admission

Filteau J et al, *Drug and Alcohol Dependence* 2018; 185:313-21
• First Nations children are disproportionally affected.

• Urine or meconium toxicology screens are rarely used, the decision to conduct toxicology screens requires maternal consent.

• Modified Finnegan score remains the recommended “standard”, despite well known limitations.

• Rooming-in model of care can be considered for mother-infant dyads when infants are term or near term, medically stable, and adequate resources are in place to support both families and HCP.

• Nonpharmacological interventions, including breastfeeding, are recommended and should be initiated promptly.

• Morphine or methadone are the recommended first-line medication.

• Pharmacological tapering in an outpatient setting is an option for a selected group.
• Morphine hydrochloride, 1 mg/ml, contains 4.8% alcohol.
• Alcohol-free Morphine solution no longer available in Canada.
• Clonidine, oral liquid, 0.01 or 0.1 mg/ml, compounded at local hospital pharmacy (only available as tablets in Canada).
• Methadone, oral liquid, 1 mg/ml, not compounded. Special education and training to prescribe methadone required by several Provincial Colleges of Physicians (but Federal Exemption no longer (2019) required.
• Buprenorphine: no formulation workable in Canada (only available as patch or in combination with naloxone, smallest tablets are 2 mg).
Main results of a recent (2018) national survey

- Canadian Pediatric Surveillance Program, 2,808 pediatricians and neonatologists surveyed across Canada, 31% response rate (n=878).
- 90% use Finnegan Score or Modified Finnegan Score for screening and monitoring.
- 46% have access to rooming-in setting and 80% support rooming-in practices.
- Morphine is almost always used as first line of treatment. Clonidine or Phenobarbital are equally used as second line.
- 64% rely on locally developed guidelines, 29% use the CPS practice point as a resource for management guidance.
- Monitoring concerns and lack of resources (education material and staff) are the recognized main barriers for centres not offering rooming-in facilities.
Panelist

Merran Thomson
Optimizing Clinical Trials for Neonatal Opioid Withdrawal Syndrome (NOWS) and Neonatal Abstinence Syndrome (NAS)

International Experiences and Models of Care – EUROPE

Merran Thomson
“Defining the problem” – understanding NOWS in Europe

• What is Europe?

• Are there European guidance / recommendations?

• What data is collected and publicly available in the English language?

• Are there common themes and strategies for managing substance misuse / dependency in pregnancy and for babies with NOWS?
What is Europe?

- WHO – 53 countries
- EU – 28 countries
- “Conventional” Europe

United Nations – 44 countries
Are there European guidance / recommendations?

- Screen and Identify early
- Psychological support
- Pharmacological treatment (maintenance and relapse prevention)
- Methadone > Buprenorphine

EMCDDA PAPERS
Pregnancy and opioid use: strategies for treatment

Practices, service provision, legal and social implications vary significantly across Europe

What about the baby?
- Very little known
- Not covered by EMCDA
- ? National guidelines for Rx
- Anecdotally neonatologists report:
  - NOWS follows primarily illicit opioid use (Heroin)
  - Frequently associated with polysubstance exposure in utero
  - Morphine probably the most commonly used
What data is collected and publicly available?

**European Drug Report 2018**


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**Estimated annual prevalence of high-risk opioid use**

Cases per 1,000 population

- **0–2.5**
- **2.51–5.0**
- **>5.0**
- **No data**

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**AT A GLANCE — ESTIMATES OF DRUG USE IN THE EUROPEAN UNION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Last year use</th>
<th>Lifetime use</th>
<th>High risk opioid use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (15–64)</td>
<td>24.0 million</td>
<td>87.6 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
<td></td>
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<tr>
<td>Young adults (15–34)</td>
<td>17.2 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
<td></td>
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<tr>
<td><strong>Cocaine</strong></td>
<td></td>
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<tr>
<td>Adults (15–64)</td>
<td>3.5 million</td>
<td>17.0 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td>Young adults (15–34)</td>
<td>2.3 million</td>
<td></td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td><strong>MDMA</strong></td>
<td></td>
<td></td>
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<tr>
<td>Adults (15–64)</td>
<td>2.6 million</td>
<td>13.5 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td>Young adults (15–34)</td>
<td>2.2 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td><strong>Amphetamines</strong></td>
<td></td>
<td></td>
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<tr>
<td>Adults (15–64)</td>
<td>1.7 million</td>
<td>11.9 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td>Young adults (15–34)</td>
<td>1.2 million</td>
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<tr>
<td></td>
<td>Last year use</td>
<td>Lifetime use</td>
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<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
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<tr>
<td>High risk opioid users</td>
<td>1.3 million</td>
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<tr>
<td></td>
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<tr>
<td>Drug treatment requests</td>
<td>628,000</td>
<td></td>
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<tr>
<td>Fatal overdoses</td>
<td>36%</td>
<td>84%</td>
<td></td>
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</tbody>
</table>

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For the complete set of data and information on the methodology, see the accompanying online Statistical Bulletin.
What data is collected and publicly available?

European Drug Report 2018
What data is collected and publicly available?

- Substance use in pregnancy
  - Very little data available
  - Most recent national Scotland

**EU + Norway and Turkey**

Data on drug use among pregnant women
- Not available for most European countries
- Often comes from isolated studies using various methodologies
- Results are not readily comparable
- 2018 European Drug Report does not mention pregnancy or NAS
- “Each year in Europe approximately 30 000 pregnant women use opioids and a similar number have other drug problems”.

Source: SMR02 ISD Scotland IR2017-01969
Are there common themes and strategies across Europe?

- Opioid dependency is a common problem*
- The pattern of misuse varies widely across Europe
- The number of newborns exposed to opioids in utero is not known
- The number of newborns experiencing opioid withdrawal is not known
- European Monitoring Centre for Drugs and Drug Addiction has produced a guide on strategies for the care and treatment of women using opioids in pregnancy, BUT the extent of care provision in individual countries is unknown
- There is no requirement for countries to collect data on NOWS and it appears the majority do not record the prevalence of NOWS

* UNODC Reported rates of use in adult population: Serbia 5%, Czech Republic 2.6%, and between 1-2% of many European countries

https://dataunodc.un.org/drugs/prevalence_map
Epidemiology of NAS - Australia

Year of Birth

Percentage of all births

Heroin Drought

Methamphetamines
Mothers are getting older
• Guidelines first developed 2006
• Free health care
• Harm minimization
• Aim: stabilize mother
• Recommendations:
  • Rooming in
  • Breast feeding
  • Morphine +/- phenobarbitone
  • Minimum hospitalization 5 days (mean 10d)
• Follow-up 1-2 years:
  • Home visiting
  • Outpatient NAS medication weaning
  • Eye, developmental and hepatitis checks by 1 year
Retrospective study found that outpatient care for infants exposed to drugs during pregnancy was sustainable and safe

R Rasul¹, M Ward¹², S Clews³, J Falconer³, J Feller⁴, K Lui¹², J Oei (joei@unsw.edu.au)¹²

1. School of Women’s and Children’s Health, University of New South Wales, Kensington, NSW, Australia
2. The Royal Hospital for Women, Randwick, NSW, Australia
3. The Langton Centre, Sunny Hills, NSW, Australia
4. Sydney Children’s Hospital, Randwick, NSW, Australia

- Retrospective review of outpatient service at Sydney Children’s Hospital, Randwick, Australia
- 774 mother/infant pairs 1998-2016
- Median LOS 7 days
- 83% discharged home on morphine (76 days, IQR 35-120, 11,499 outpatient treatment days)
- 3 medication errors (morphine weaned faster than prescribed, 2x extra dose phenobarbitone)
- No deaths while on NAS medications
- 5 deaths (1x drowned in bathtub, 4x SIDS, none while medicated)
- No readmissions for withdrawal
The 2019 International Neonatal Consortium Neonatal Scientific Workshop

Optimizing Clinical Trials for Neonatal Opioid Withdrawal Syndrome (NOWS) and Neonatal Abstinence Syndrome (NAS)

Hendrée Jones, PhD
Executive Director, Horizons Program
Professor, Department of Obstetrics and Gynecology
School of Medicine, University of North Carolina at Chapel Hill

10:30-12:30
May 2, 2019
Regency I&II
Issues in NOW/NAS Assessment

• Diagnosis

• Severity

• Response to Treatment

Early 1800’s: Increased use of opioid use by women

1875: Infant in withdrawal recorded

1894: “Congenital Morphinism” 12 cases/ 9 died

1950’s: NAS term coined- treatments = Chlorpromazine, morphine, methadone, phenobarbital or paregoric

1974: ADAMHA (NIDA) research on medication treatment for opioid use disorders during pregnancy

1975: Finnegan and Lipsitz published NAS assessment tools

Historical Context

Kaltenbach K and Finnegan L. Chapter 14 In Opioid-use Disorders in Pregnancy (ED: T Wright) Cambridge UP, 2018
Drugs Involved in Overdose Deaths, 2000-2016

Note: 2016 figures are provisional and cover the 12-month period ending in January 2017.
Source: Centers for Disease Control and Prevention

Winkelman et al. *Pediatrics*, 2018
Results when a pregnant woman regularly uses opioids (e.g., heroin, oxycodone) during pregnancy

NAS defined by alterations in the:

- **Central nervous system**
  - high-pitched crying, irritability
  - exaggerated reflexes, tremors and tight muscles
  - sleep disturbances

- **Autonomic nervous system**
  - sweating, fever, yawning, and sneezing

- **Gastrointestinal distress**
  - poor feeding, vomiting and loose stools

- **Signs of respiratory distress**
  - nasal congestion and rapid breathing

- **Newborns cannot be “born addicted”**

- **NAS is not** Fetal Alcohol Syndrome (FAS) only FAS has confirmed long term physical, cognitive and behavioral effects

- **NAS is treatable**

- **Interactions between the caregiver and child** can impact resiliency/risk with potential long-term effects in some cases

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e.g., Finnegan et al., Addict Dis, 1975; Desmond & Wilson, Addict Dis, 1975; Jones & Fielder, Preventive Medicine, 2015.
It is essential that infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage, and anoxia be ruled out as the cause of the signs.
NOW/NAS Assessment: Diagnosis

• NAS traditionally described as percent of babies needing treatment (29-94%)
  
  • Lack of consistent definition
  
  • ICD-9 hospital codes of neonatal drug withdrawal
  
  • NAS not differentiated based on type of drugs (heroin, misuse prescription misuse vs appropriate maternal use under MD care)
  
  • What risk is comparable the overall risk to fetus and neonate may differ widely
  
  • Morbidity and mortality rates in pregnancy and newborns are reduced with medication assisted treatment, prenatal care and comprehensive services

# NAS: Various Substances

## Neonatal Abstinence Syndrome

### TABLE 1 Onset, Duration, and Frequency of NAS Caused by Various Substances

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset, h</th>
<th>Frequency, %</th>
<th>Duration, d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heroin</td>
<td>24–48</td>
<td>40–80(^{27})</td>
<td>8–10</td>
</tr>
<tr>
<td>Methadone</td>
<td>48–72</td>
<td>13–94(^{27})</td>
<td>Up to 30 or more</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>36–60</td>
<td>22–67(^{46,48})</td>
<td>Up to 28 or more</td>
</tr>
<tr>
<td>Prescription opioid medications</td>
<td>36–72</td>
<td>5–20(^{66,69})</td>
<td>10–30</td>
</tr>
<tr>
<td><strong>Nonopioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>24–48</td>
<td>20–30(^{94})</td>
<td>2–6</td>
</tr>
<tr>
<td>TCAs</td>
<td>24–48</td>
<td>20–50(^{94})</td>
<td>2–6</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>24</td>
<td>2–49(^{91})</td>
<td>7–10</td>
</tr>
<tr>
<td>Inhalants</td>
<td>24–48</td>
<td>48(^{70})</td>
<td>2–7</td>
</tr>
</tbody>
</table>
NAS Severity: Pre-delivery Factors

Other factors that contribute to NAS, need for medication, and length of stay in neonates exposed to opioid agonists in utero:

- Genetics
- Other Substances
  - Tobacco use
  - Benzodiazepines
  - SSRIs
- Gestational age
- Birth weight

Methadone or buprenorphine dose is not consistently related to NAS severity

Other factors that contribute to NAS, need for medication, and length of stay in neonates exposed to opioid agonists in utero:

- Presence of a protocol
- NICU setting
- The NAS assessment choice
- NAS medication choice (methadone and buprenorphine gaining attention)
- Initiation and weaning protocols
- Breastfeeding
- Mother and baby together
NAS Assessment: Tools

♦ The Neonatal Abstinence Scoring Tool “Finnegan Scale” (FNAST)
♦ Narcotic Withdrawal Score (Lipsitz Tool)
♦ The Ostrea tool
♦ Neonatal Narcotic Withdrawal Index
♦ Neonatal Withdrawal Inventory
♦ MOTHER NAS Scale- 3 item screener and a 5 item index

NAS Assessment and Response

- Common features - summing item scores and/or weighting the severity of presenting signs

- Evaluation every 3 to 4 hours during hospitalization

- Scores above a threshold trigger medication initiation to reduce NAS severity – no or delayed treatment can result in morbidity or mortality

- Stabilization on medication promotes regular eating and sleeping patterns, weight gain, and improved interaction with caregivers

- Medication amount is increased then gradually decreased until the neonate is stable without medication

**Eat, Sleep and Console**

- N=50 consecutive opioid-exposed infants had FNASS scores recorded every 2 to 6 hours but were managed by using the Eat, Sleep, Console (ESC) assessment approach.

- Actual treatment decisions made by using the ESC approach were compared with predicted treatment decisions based on recorded FNASS scores.

- ESC approach, 6 infants (12%) were treated with morphine compared with 31 infants (62%) predicted to be treated with morphine by using the FNASS approach ($P < .001$).

- There were no readmissions or adverse events reported.

**Other Novel Approaches**

- Pupil diameter
- Skin conductance
- Sleep states
- Fetal functioning

Summary Recommendations

- Defining NAS needs further study
- NAS assessment tools needs to be disentangled from treatment strategies
- Current outcomes are focused on care utilization (e.g., dollars spent in NICU, Proportion of infants treated for NAS; length of hospital stay, days of medication received, total amount of medication received)
- More patient-centered outcomes are needed (e.g. how to best measure stress the infant undergoes due to NAS and/or its treatment?)
- What methods can help caregivers and parents reduce infants stress, improve bonding and prevent ACES?
- Patients and the providers who treat them will be best served through having a validated screening, assessment and then tailored treatment options from which to optimize care
Withdrawal Symptoms that Contribute to the Decision to Treat

Norma Terrin, PhD
• FNAST is a complex and burdensome tool:
  • 21 items
  • Items have 2-4 categories
  • Weighting for each category varies between 1 and 5
• Infants’ withdrawal symptoms must be assessed every few hours
• We sought to answer:
  • Which items contribute most to the decision to treat?
  • Is information lost by eliminating weighting and dichotomizing items?
  • Is there cohort-to-cohort variation in endorsing the items?
  • Do the items that contribute to the treatment decision correspond to the “eat-sleep-console” method?
Study Design

- Population: opioid-exposed neonates ≥36 weeks gestation
- Development sample: University of Kentucky (n=94), University of Louisville (n=127), and a multisite clinical trial and concurrent observational study led by Tufts Medical Center (n=203).
- Validation sample: Maine Medical Center (MMC, n=280).
- Study measures: Item responses from the highest FNAST score on the day pharmacologic treatment was initiated or on day 3 of life if not treated. Each item was dichotomized.
- Stepwise multivariable logistic regression was used to determine which items were independently associated with receipt of pharmacologic therapy, adjusting for cohort.
- Variation in the endorsement of specific items across cohorts was evaluated using frequencies and percentages as well as the intraclass correlation coefficient (ICC).
- Thresholds were selected for the shortened FNAST to correspond to the commonly used FNAST thresholds of 8 and 12.
- Factor analysis was used to assess whether the selected items correspond to “eat-sleep-console”
Results

- Baseline for comparison: AUC=0.90 for the model that uses the full 21-item FNAST to predict treatment
- The stepwise procedure selected 11 items - AUC=0.88
- The corresponding ICC was 0.40
- High-pitched crying was eliminated for excessive variability
- The two tremor items were combined
- The 9-item scale AUC=0.87
- Validation at MMC: AUC=0.91
## Final Model with 9 items

<table>
<thead>
<tr>
<th>Item</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeps ≤3 Hours After Feeding</td>
<td>2.9 (1.7, 5.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hyperactive Moro Reflex</td>
<td>3.6 (1.8, 7.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Tremors</td>
<td>3.7 (1.6, 8.4)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Increased Muscle Tone</td>
<td>10.4 (3.3, 33.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Respiratory Rate &gt;60/min</td>
<td>2.1 (1.2, 3.6)</td>
<td>0.0110</td>
</tr>
<tr>
<td>Excessive Sucking</td>
<td>1.9 (1.1, 3.4)</td>
<td>0.0219</td>
</tr>
<tr>
<td>Poor Feeding</td>
<td>3.1 (1.5, 6.3)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Regurgitation or Projectile Vomiting</td>
<td>4.6 (2.0, 10.6)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Loose or Watery Stools</td>
<td>2.2 (1.1, 4.1)</td>
<td>0.0175</td>
</tr>
</tbody>
</table>

Thresholds of 8 and 12 on the FNAST correspond to 4 and 6 on the 9-item tool.
• High-pitched crying was heterogeneous (77% UL, 80% UK, and 21% Tufts; ICC=0.40)

• The extreme heterogeneity of “high-pitched crying” together with its relatively low OR in the 11-item scale (OR=2.4) and minimal impact on the AUC influenced our decision to remove it.

• Moro reflex was heterogeneous (28% UL, 68% UK, and 17% Tufts; ICC=0.28).

• The other items in the 9-item scale were also heterogeneous but ICC’s were lower (0.12 or lower)
## Factor Analysis Does Not Support Eat-Sleep-Console

<table>
<thead>
<tr>
<th>Rotated Factor Pattern</th>
<th>Factor1</th>
<th>Factor2</th>
<th>Factor3</th>
<th>Factor4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Muscle Tone</td>
<td>0.74185</td>
<td>0.03796</td>
<td>-0.04269</td>
<td>-0.08875</td>
</tr>
<tr>
<td>Tremors</td>
<td>0.72894</td>
<td>0.04195</td>
<td>0.01518</td>
<td>0.13585</td>
</tr>
<tr>
<td>Hyperactive Moro Reflex</td>
<td>0.49050</td>
<td>0.11338</td>
<td>0.21762</td>
<td>-0.00643</td>
</tr>
<tr>
<td>Respiratory Rate &gt;60/min</td>
<td>0.05156</td>
<td>0.73345</td>
<td>0.04511</td>
<td>-0.17181</td>
</tr>
<tr>
<td>Excessive Sucking</td>
<td>0.16921</td>
<td>0.67843</td>
<td>-0.15372</td>
<td>0.13518</td>
</tr>
<tr>
<td>Sleeps &lt;3 Hours After Feeding</td>
<td>-0.04906</td>
<td>0.51235</td>
<td>0.28116</td>
<td>0.47563</td>
</tr>
<tr>
<td>Regurgitation or Projectile Vomiting</td>
<td>0.08272</td>
<td>-0.16686</td>
<td>0.76562</td>
<td>0.06916</td>
</tr>
<tr>
<td>Poor Feeding</td>
<td>0.05826</td>
<td>0.11591</td>
<td>0.70261</td>
<td>-0.10194</td>
</tr>
<tr>
<td>Loose or Watery Stools</td>
<td>0.04602</td>
<td>-0.04829</td>
<td>-0.10306</td>
<td>0.87543</td>
</tr>
</tbody>
</table>

**Eat:** factor 3 😊  
**Sleep:** Splits between factors 2 and 4 😐  
**Console:** Factor 1? Factor 2? Can there be 2 orthogonal meanings of “console?” 😐
Conclusions

- Nine binary items accounted for nearly all of the variation in the decision to treat
- The items predict treatment despite variation in the treatment algorithm among the cohorts
  - two consecutive 8’s or one 12: Tufts
  - three consecutive 8’s or two 12’s: UL and UK
- The items did not lose predictive power in a validation sample
- There is cohort-to-cohort heterogeneity in endorsement of items (especially high-pitched crying), some of which is likely due to subjective interpretation by assessors
- Variation in withdrawal symptoms is not entirely explained by the eat-sleep-console paradigm
Collaborators

• Lori A. Devlin
• Janis L. Breeze
• Enrique Gomez
• Barry Lester
• Loretta Finnegan
• Alexa Craig
• Jonathan M. Davis
Regulatory Challenges in the Drug Development for NOWS

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Medical Officer, Addiction Products
FDA Division of Anesthesia, Analgesia, and Addiction Products
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Challenges in Clinical Trial Drug Development for NOWS Treatment

1. Available Treatments and Approaches to Care
2. Current Drug Formulation Issues
3. New Drug Formulation Development for NOWS
4. Designing NOWS Clinical Trials
1. Available Treatments & Approaches to Care

- Pediatric development programs often rely on extrapolation from adult findings
- Drugs used to treat withdrawal in adults currently provide limited data for NOWS treatment:
  - methadone (DESI indication)
  - buprenorphine (not specifically labeled for detoxification)
  - clonidine (off-label)
  - Currently, there is one marketed approved drug for treating symptoms of abrupt opioid withdrawal in adults: Lucemyra.
- The lack of approved adult products for withdrawal treatment makes conclusions about appropriate pediatric dosing difficult
2. Drug Formulation Issues

- “Why can’t I use an available drug as-is for a neonate?”
  - Chemistry and manufacturing concerns
- In NOWS literature, studies have been conducted with various formulations and ‘Standard of Care’ is not standardized
  - details of the formulations and how they are prepared might not be provided
- Not all drug products are formulated the same way:
  - Approved Commercial Formulations
    - FDA approval ensures uniformity of the drug product: identity, quality, purity, strength, stability
  - Compounded and Extemporaneous Formulations
    - MANY sources of inconsistency
  - Marketed Unapproved Formulations
    - No FDA assurances
3. Challenges in NOWS Drug Development: 

**Liquid Formulations**

- Palatability (taste, texture, smell)
- Route of administration and bioequivalence:
  - Creating a drug for a population unable to swallow tablets/capsules (e.g., liquid)
- Proper Measuring Device(s)
- Suitable Container/Closures (leachable/extractables)
- Physical and Chemical Stability of Ready to Use Solution or Suspension
- Choice of Excipients (safety considerations – potential toxicity)
### 3. Challenges in NOWS Drug Development: Excipient Toxicity in Young Children

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Administration</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl alcohol</td>
<td>Oral, parenteral</td>
<td>Neurotoxicity, metabolic acidosis</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Oral, parenteral</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Parenteral</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>Parenteral</td>
<td>Liver &amp; kidney failure</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Parenteral</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Oral, parenteral</td>
<td>Seizures, neurotoxicity, hyperosmolarity</td>
</tr>
</tbody>
</table>
3. Challenges in NOWS Drug Development:

**Drug Formulation Stability Issues**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Issue</th>
</tr>
</thead>
</table>
| Solution                     | • Precipitation  
• Discoloration  
• Degradation  
• **Loss of potency** |
| Sterile Formulations         | • **Microbial**  
• Endotoxin testing/Sterility/ Particulate matter |
| Powder for Oral Suspension   | • **caking** - difficulty in dispersing the powder upon reconstitution |
| Tablet                       | • **loss of potency**  
• chewable tablet hardening  
• friability |
3. Example of Stability Issue: Zenpep (pancrealipase)

- Lipase capsule; indicated for infants ≤ 12 months
- Contents of capsule may be sprinkled on soft acidic food such as apple sauce
- Contents should **not** be mixed directly into formula or breast milk

---

### 2.2 Administration

Zenpep should always be taken as prescribed by a healthcare professional.

**Infants (up to 12 months)**

Zenpep should be administered to infants immediately prior to each feeding, using a dosage of 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. Contents of the capsule may be administered with a small amount of applesauce, or other acidic food with a pH of 4.5 or less (e.g., commercially available preparations of bananas, or pears). Contents of the capsule may also be administered directly to the mouth. Administration should be followed by breast milk or formula. Contents of the capsule should not be mixed directly into formula or breast milk as this may diminish efficacy. Care should be taken to ensure that Zenpep is not crushed or chewed or retained in the mouth, to avoid irritation of the oral mucosa.

**Children and Adults**

Zenpep should be taken during meals or snacks, with sufficient fluid. **Zenpep capsules and capsule contents should not be crushed or chewed.** Capsules should be swallowed whole.

For patients who are unable to swallow intact capsules, the capsules may be carefully opened and the contents sprinkled on small amounts of acidic soft food of pH 4.5 or less (e.g., commercially available preparations of bananas, pears and applesauce).

The Zenpep-soft food mixture should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.

*Source: section 2.2 of Zenpep drug label*
4. Challenges in the Design and Interpretation of NOWS Clinical Trials

• Literature in NOWS:
  – Studies conducted with various formulations have been published
  – Often, details of the formulation and how it is prepared and doses are not provided

• Clinical Practice in NOWS:
  – Clinical care employs compounded, extemporaneous, and marketed unapproved formulations (stability issues)
  – Lack of standardization makes conclusions about appropriate dosing difficult
4. Challenges in the Design of NOWS Clinical Trials

- Defining the population
- Assessment tools
- Primary Outcome Measures
  - Length of stay
  - Length of treatment
  - Need for medication
- Comparators
  - No approved regimens using approved commercial formulations exist
  - Is it acceptable to be non-inferior to a ‘standard of care’ regimen?
Thank you
FDA Guidelines for Pediatric Drug Development

- Reflects current thinking about how drugs should be developed and labeled for the pediatric population

https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf (Clinical pharmacology)
A Clinical Trialist’s Perspective on Harmonization of Trial Elements

Walter K. Kraft, MD
Thomas Jefferson University
Philadelphia, PA
Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science.

INC is ...a global collaboration formed to forge a predictable regulatory path for evaluating the safety and effectiveness of therapies for neonates.

- Clinical trials up to now have not been registration seeking
- Interface with FDA has primarily been around IND
- To maximize utility, trials should assume a registration mindset
• In utero opioids are primary drivers of symptomatology
• An opioid is the base pharmacologic therapy
• All infants should have maximized non-pharm bundle
• Current symptom instruments are insensitive in assessing non-opioid withdrawal
Progress of past decade

• High quality RCTs
• Real world evidence
• Standardization of care
  • Institutional protocols
  • Statewide collaboratives
• Descriptive pharmacometrics
  • Clonidine
  • Methadone*
  • Buprenorphine
  • Morphine
Endpoints

• Current endpoints (efficacy)
  • Duration of treatment
  • Length of stay
  • Need for adjunctive treatment
  • Readmission rates
  • PK, pharmacogenetics, effectiveness

• Long term measures (safety)
  • Neurodevelopment
  • Duration
  • Availability-assessment bias
  • Biologic basis for concern?
Inclusion Criteria: NOWS vs NAS

- Gestational age 36+ wks
- Other exposures
  - Benzodiazepines
  - SSRI
  - Antipsychotics
  - Gabapentin
  - Tobacco
- Maternal stability as covariate
  - Methadone dose
  - Illicit drug use
- Willingness to participate—bias?
Study Design

• Pragmatic vs traditional RCT
  • Site capacity

• Superiority vs non-inferiority

*Depends upon the question being asked*
Drug vs Regimen

• No standard regimen
  • Weight vs symptom based
  • PRN only regimens
  • Any trial will require change in local practice
• Adjunct agent
  • Symptoms despite high dose opioid
  • Start early or late?
  • In parallel as opioid sparing

Lack of standard is also an opportunity
**Endpoints**: Defining what, if any, developmental outcomes should be prioritized

**Study populations**: Inclusion criteria to balance measurements of efficacy and effectiveness

**Instruments**: Assisting with evaluation of existing and novel scoring devices

**Data elements**: Harmonization of data elements for both RCT and real world evidence

**Formulations**: Assist with issues around local compounding, stability, bioavailability

**Defining natural history**: Supporting disease state models
Developing Core Data Elements

Lauren Kelly PhD, MSc, CCRP
Children’s Hospital Research Institute of Manitoba
University of Manitoba

May 2, 2019
Neonatal response to opioid exposure in pregnancy is not a one size fits all model.

In order to predict which babies will require treatment we need to details about the exposure.

To build and validate risk prediction models we need large amounts of data which means collaborating across multiple sites and countries.

Are sites collecting the same information?
Example of core data elements

• Population
  • Demographics including maternal variables
  • Diagnosis
  • Assessment
• Definitions for non-pharmacologic management
• Breastfeeding, rooming-in and discharge policies
• Criteria for treatment
• Treatment type, starting dose, weaning schedule
• Adjuvant treatment
• Outcome measures.....
A core outcome set for neonatal abstinence syndrome: study protocol for a systematic review, parent interviews and a Delphi survey

What outcomes matter to parents?

Number of parents reporting outcome as important (N = 6)
A core outcome set for NAS/NOWS

1. Consolability
2. Difficulties feeding
3. Parent-infant bonding
4. Neurodevelopmental outcomes
5. Readmission to hospital for NAS/NOWS concerns following discharge
6. Receiving any breastmilk at discharge
7. Weight gain
8. Time to adequate symptom control
9. Required treatment:
   a) Need for pharmacological treatment to manage withdrawal
   b) Dose (total amount in mg) of treatment provided
   c) Length of treatment
   d) Treatment with more than one medication
Conclusions

• To compare/contrast studies or to build a NAS/NOWS data registry we need to be sure we are recording and measuring the same thing across multiple centres and countries

• We need to know:
  • What is already being captured and how this data is defined?
  • What data is important to Parents? Clinicians? Researchers? Policy makers? Regulators?

• Rigorous and diverse stakeholder engagement is critical to meaningfully improving the quality of research in NAS/NOWS

Lauren.Kelly@umanitoba.ca
Twitter: @PharmaLauren
Parent Perspective

Victoria Kuck
Thank You
Potential Discussion Questions

• For parents and for hospital staff, what improvements in the disease process would be most clinically meaningful? (e.g. shorter pharmacologic treatment duration, faster time to symptom control, improved feeding capability....)
• What are the most urgent needs for designing trials for NOWS/NAS?
• What are the most critical knowledge gaps in the science (clinical and nonclinical)?
• Are there early developmental evaluations (at discharge or in the first year) that could be informative relative to treatment safety?
• What information can be obtained from long-term developmental and behavioral outcome studies? Are conclusions about treatment effects possible, when the impact of home environment is so powerful?
• What can we tell parents based on the information about long-term outcomes that is already available?