FDA ADVISORY COMMITTEE: Neonatal Opioid Withdrawal Syndrome

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June 8, 2015
Disclosures:

• I will discuss off-label uses of medications
• I have no financial disclosures

However, I am a Canadian, eh?
Neonatal Opioid Withdrawal Syndrome (NOWS): Objectives

- Historical context
- Current context
- Pathophysiology
- Signs and symptoms of NOWS
- Factors affecting the incidence and severity of NOWS
- Management
- Outcomes
- UVM Experience
Neonatal Abstinence Syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome (NOWS) often results when a pregnant woman uses opioids (e.g., heroin, oxycodone) during pregnancy.

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 stuffiness and rapid breathing

NAS is not Fetal Alcohol Syndrome (FAS)

NAS is treatable

(Finnegan et al., Addict Dis. 1975; Desmond & Wilson, Addict Dis. 1975)
NOWS: Historical Context

- 1875 to 1900 multiple reports of congenital morphinism – most died, no specific treatment offered
- 1903 report about congenital morphinism – treated infant with morphine
- 1964 Methadone introduced as pharmacotherapy
- 1965 Goodriend et al report neonatal withdrawal signs
- 1971 Zelson et al reported frequency of signs on neonatal withdrawal in 259 of 384 infants born to drug-abusing mothers
- 1975 Desmond and Wilson publish Neonatal Abstinence Syndrome: Recognition and Diagnosis
- 1975 Finnegan et al publish neonatal abstinence syndrome tool
NOWS: Current Context

2012:
- 21,732 newborns
- ~$1.5 billion
- 81.5% Medicaid
- ↑ complications

Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012
Patrick et al, J of Perinatology, 2015
NOWS: Current Context

Issues facing substance-using pregnant women and their children

- Generational substance use
- Gender inequality/male-focused society
- Limited parenting skills and resources
- Exposure to trauma
- Legal involvement
- Unstable housing
- Unstable transportation
- Lack of positive and supportive relationships

Slide courtesy of H Jones
The untreated woman with opioid-use disorder who becomes pregnant: neonatal effects

- Neonatal opioid withdrawal
- Neonatal complications
  - Meconium aspiration, transient tachypnea
  - Feeding difficulty, seizures, jaundice
- If recognized that mother is opioid-dependent
  - Child protective services involvement
  - Challenge of taking care of newborn and starting treatment for addiction
- If unrecognized and infant exhibits no withdrawal
  - After discharge infant may be particularly irritable
  - Family’s ability to cope and seek help impeded by fear of discovery
  - Mother will probably remain active in her addiction
  - Exposure of infant to unsafe situations
  - Mother continuously “flying under the radar” and hiding her addiction
  - Mother often unwilling to come forward for fear of losing her child/children
Medication Assisted Treatment (MAT): Standard of Care for Pregnancy

• WHO 2014: “Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment…rather than…attempt opioid detoxification.”

• Facilitates retention of mothers/infants with decreased use of illicit substances when compared to no medication

• MAT results in NOWS which needs Rx in 50-60% patients (Jones et al, 2010)

• There is no evidence for the dose of methadone affecting the incidence of NOWS (Cleary et al, 2010; Jones et al., 2013)
NAS ≠ NAS ≠ NAS

NAS Profile

- Drugs
- Alcohol
- Tobacco
- SSRIs
Pathophysiology of Neonatal Opioid Withdrawal

- **↑ Acetylcholine**
  - Diarrhea, vomiting
  - Yawning
  - Sneezing, sweating
  - Sweating

- **↓ Serotonin**
  - Sleep deprivation
  - Sleep fragmentation

- **↑ Other receptor activity**
  - Hyperalgesia
  - Allodynia

- **↓ Lack of opioids in chronically stimulated receptors**
  - Super activation of cyclic AMP
  - Increased protein kinase
  - Increased transcription factors
  - Increased release of neurotransmitters

- **↑ Noradrenaline**
  - Hyperthermia
  - Hypertension
  - Tremors
  - Tachycardia

- **↓ Dopamine**
  - Hyperirritability
  - Anxiety

- **↑ Corticotropin**
  - Increased stress
  - Hyperphagia

Adapted from Prabhakar Kocherlakota Pediatrics 2014;134:e547-e561
NOWS: Signs and Symptoms

• Signs of withdrawal typically start after 24-96 hours after birth depending upon the specific opioid exposure
• Central nervous system signs
  • Tremors
  • Irritability, high-pitched crying
  • Sleep disturbances
  • Tight muscles tone, hyperactive reflexes
  • Myoclonic jerks (sometimes misinterpreted as seizures), seizures - rare
• Autonomic signs
  • Sweating, fever, yawning and sneezing
  • Rapid breathing, nasal congestion
• Gastrointestinal signs
  • Poor feeding, vomiting and loose stools or diarrhea

What would happen if NOWS is untreated?
• Depends upon the severity
• There are many infants who do not receive medication for NOWS and their outcome is good
• However, an irritable, crying baby who does not sleep and cannot feed will be at risk for
  • Dehydration
  • Abusive trauma
  • Interrupted attachment and maybe failure of attachment
• Excessive irritability and dehydration are very likely to lead the caregiver to seek medical attention
• An infant may die without treatment – however, in an extensive literature search, the only reported deaths occurred over 100 years ago
• NOWS does not lead to poor neurodevelopmental outcomes
Scoring tools for NOWS/NAS

- Finnegan Neonatal Abstinence Scoring System
  - 31 items
  - Symptoms are weighted
  - Guidelines for pharmacologic treatment at score of 8 or greater
- MOTHER score (modified Finnegan score)
  - 19 items (which contribute to total score)
  - Items weighted differently
  - Some items eliminated and others added
  - Guidelines for treatment based on score rather than weight
- Lipsitz Neonatal Drug-Withdrawal Scoring System
  - 11 items
  - Items scored for severity and gives guidelines for treatment
- The Neonatal Withdrawal Inventory – 8 point checklist
- The Neonatal Narcotic Withdrawal Index – 6 signs plus others
NAS Assessment: MOTHER NAS Scale

- NAS score is not the sole determining factor in the decision to start starting Rx
- Score can be affected by:
  - State of infant
  - Painful stimuli
  - Order of score
  - “Motive” of scorer

<table>
<thead>
<tr>
<th>Score</th>
<th>Crying: excessive high pitched</th>
<th>Crying: Continuous high pitched</th>
<th>Sleeps &lt; 1 hour after feeding</th>
<th>Sleeps = 2 hours after feeding</th>
<th>Sleeps &gt; 3 hours after feeding</th>
<th>Hyperactive Moro Reflex</th>
<th>Markedly Hyperactive Moro Reflex</th>
<th>Mild Tremors: Disturbed</th>
<th>Moderate-Severe Tremors: Disturbed</th>
<th>Mild Tremors: Undisturbed</th>
<th>Moderate-Severe Tremors: Undisturbed</th>
<th>Myoclonic jerks</th>
<th>Increased Muscle Tone</th>
<th>1-2</th>
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<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<td>1</td>
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</tr>
<tr>
<td>Score</td>
<td>Excessive irritability</td>
<td>Nasal Stufiness</td>
<td>Tussing (4 or more successive times)</td>
<td>Tachypnea (Respiratory Rate &gt; 60/min)</td>
<td>Retractment</td>
<td>Nasal Flaring</td>
<td>Poor feeding</td>
<td>Excessive stooling</td>
<td>Vomiting (or regurgitation)</td>
<td>Projectile vomiting</td>
<td>Loose Stools</td>
<td>Watery Stools</td>
<td>Failure to Thrive (Current weight &gt; 10% below birth weight) &gt; 90% BW?</td>
<td>Total score</td>
</tr>
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<td>present/absent</td>
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<table>
<thead>
<tr>
<th>INITIALS OF SCORER</th>
<th>Courtesy of H Jones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological Management:</td>
<td>Morphine Maintenance</td>
</tr>
<tr>
<td>Maintenance dose if score 0-8</td>
<td>Increase dose by 0.02 if score is 9-12 (rescore before dosing)</td>
</tr>
<tr>
<td>Increase dose by 0.04 if score 13-16</td>
<td>Increase score by 0.06 if score 17-20</td>
</tr>
</tbody>
</table>

Weaning Instructions:
- Maintain on dose 8 hrs before starting weaning
- Wean 0.02 mg morphine every day for a score is 0-8
- Refer wean for score 9-12
- Re-escalation:
  - If rescore of 9-12 re-score as described for initiation
  - If second score is in 9-12 increase morphine 0.01 mg q3-4 hrs
  - If 2 consecutive scores 13-16, increase 0.02 mg q3-4 hrs
  - If 3 consecutive scores in 13-20, increase 0.04 mg q3-4 hrs etc
Factors affecting NOWS

- **Substances**
  - Nicotine
  - Benzodiazepines
  - SSRIs

- **Single gene polymorphisms**

- **Hospital protocols and education of the staff, breastfeeding support**
NOWS: Management

- Admit to Mother/Baby Unit – rooming-in if possible
- Minimum stay of 4-5 days to allow for symptoms to peak (onset of withdrawal in buprenorphine exposed infants is later than with methadone exposed infants)
- Utilize non-pharmacologic treatment as available
- Encourage breastfeeding
- Encourage mother to participate in the assessment of the newborn
- Role of drug testing in the infant (?)
- Crucial: excellent multidisciplinary communication
**NOWS: Non-pharmacologic Treatment**

- Breastfeeding is associated with reduced severity of withdrawal, delayed onset, decreased need for Rx (Abdel-Latif et al, 2006)
- Rooming-in decreased the need for Rx, length of Rx, and LOS (Abrahams et al, 2007)
- Water beds decreased amount of medication needed (Oro et al, 1988)
- Acupuncture (Filippelli et al, 2012)
- Kangaroo therapy or skin to skin
- Decreased environmental stimuli
- Frequent small demand feeds
- Pacifiers
- Swaddling, containment, holding, vertical rocking
- Provider, nursing attitudes
NOWS: Pharmacologic Treatment

- Short-acting opioids (morphine sulfate, dilute tincture of opium)
  - Inpatient treatment
  - "standard of care"
  - Symptom based versus weight based
  - Endorsed by the AAP (2012)

- Methadone
  - Inpatient treatment and inpatient to outpatient treatment
  - Symptom versus weight based
  - Allows for shorter length of stay (with outpatient treatment)
  - Endorsed by the AAP (2012)
  - (Several studies including MS Brown et al (2015) which revealed shortened duration of treatment with methadone)

- Dilute tincture of opium and phenobarbital (Coyle et al, 2002)
  - Decreased severity of withdrawal, decreased length of stay

- Buprenorphine (Kraft et al, 2011)
  - Shorter length of stay in buprenorphine treated infants
  - Well tolerated

- Adjunctive therapy with clonidine (Agthe et al, 2009)
  - Oral clonidine as adjunct to short-acting opioids
  - Shortens the duration of therapy, no short-term cardiovascular side effects were observed
Psychomotor in opioid and non-opioid exposed infants

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Subgroup</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>Hunt (2008)</td>
<td>1.5 years old</td>
<td>BSID (Psychomotor)</td>
</tr>
<tr>
<td>Burlowski (1998)</td>
<td>1 year old</td>
<td>GDS (Locomotor)</td>
</tr>
<tr>
<td>Moe (2002)</td>
<td>1 year old</td>
<td>BSID (Psychomotor)</td>
</tr>
<tr>
<td>Hans (2001)</td>
<td>1 year old</td>
<td>BSID (Psychomotor)</td>
</tr>
<tr>
<td>Hans (2001)</td>
<td>2 years old</td>
<td>BSID (Psychomotor)</td>
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Cognition in opioid and non-opioid exposed infants

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<td>2 years old</td>
<td>BSID (Mental)</td>
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# Outcomes: Baldacchino et al, BMC Psychiatry 2014

## Cognition in opioid and non-opioid exposed infants

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<tbody>
<tr>
<td>Hunt (2008)</td>
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<tr>
<td>Ornoy (2001/2003)</td>
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<td>McCarthy</td>
</tr>
<tr>
<td>Moe (2002)</td>
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<td>McCarthy</td>
</tr>
<tr>
<td>Walhord (2007)</td>
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<td>McCarthy</td>
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### Psychomotor in opioid and non-opioid exposed infants

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<td>Hunt (2008)</td>
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<td>Ornoy (2001/2003)</td>
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### Behaviour in opioid and non-opioid exposed infants

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<tr>
<td>Hunt (2008)</td>
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<td>Vineland Social Maturity</td>
</tr>
<tr>
<td>Ornoy (2001/2003)</td>
<td>5 years old</td>
<td>Achenbach</td>
</tr>
<tr>
<td>Moe (2002)</td>
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<td>Achenbach</td>
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In Annual Speech, Vermont Governor Shifts Focus to Drug Abuse

By Katherine O. Seelye Jan 8, 2014
The explosion of drugs like OxyContin has given way to a heroin epidemic ravaging the least likely corners of America – like bucolic Vermont, which has just woken up to a full-blown crisis

By DAVID AMSDEN

By David Amsden April 3, 2014
• Schedule 1 – 2 visits with NeoMed Clinic staff

• Written information (Care Notebook)

• http://www.uvm.edu/medicine/vchip/?Page=ICONcarenotebook.html

• Promote breastfeeding
"I SWEAR TO TELL THE TRUTH, THE WHOLE TRUTH, AND NOTHING BUT THE TRUTH, FROM MY PERSPECTIVE."
UVM Children’s Hospital NeoMed Experience

- Alleviation of fear
  - Care Notebook
  - You are not alone...
  - Ask them for their stories

- Respect
  - Introductions to others on the team
  - “Tell me about yourself”
  - “What are your dreams / goals”

- Recognition of strengths
  - Hearts
UVM Children’s Hospital
Why methadone for treatment of neonatal abstinence syndrome?

• Decreased frequency of dosing
• Less respiratory depression
• Less need for adjustment of dose
UVM Children’s Hospital
Benefits / risks of newborn outpatient treatment program with methadone

**Benefits**
- Length of stay reduced
- Slow wean of methadone reduces symptoms of withdrawal
- Allows for more breastfeeding success
- Empowers family

**Risks**
- Safety concerns – overdose to baby, use by others
- Long half-life may lead to “overmedication” in hospital
- Often prolonged course – are we treating normal baby irritability with methadone?
Infrastructure: what works in Vermont

- Clinic staff with ability to “track infants down”
- Close relationships with obstetrics, substance abuse treatment providers, WIC, child protective services and home health nursing
- Single pharmacy to dispense methadone
UVM Children’s Hospital NeoMed Clinic

- First NeoMed clinic visit within 1 week of discharge
- Infants requiring medication for NAS are seen at least every 2 weeks
- Infants not requiring treatment follow up monthly for the first 4 months, then every 2-4 months until 12-18 months
- Bayley III Scales at 8-10 months
- Hepatitis C antibody at 18 months for exposed infants
- Multidisciplinary approach involving primary care provider, home health, early intervention, ChARM team, and maternal substance abuse provider
• Review symptoms of “withdrawal” if any
• “Usual weans”
  • 0.02 mg every Monday and Thursday OR
  • 0.02 mg every Monday
• Provide written schedule for the weaning
• If any change in weaning schedule – first discuss with clinic
Total Opioid-exposed Newborns Followed at UVM Children’s Hospital (1,208 newborns)
UVM Children’s Hospital:
Infants born to opioid dependent women with substance abuse on **methadone** or **buprenorphine** at delivery (N = 876)
% Infants who received pharmacologic therapy
Why did pharmacologic treatment for NAS decrease?

- Better use of non-pharmacologic treatment
- Less subjectivity in NAS scoring
  - Through participating in MOTHER study
  - Decreased assumption of need for treatment
- Over time, the proportion of buprenorphine-treated pregnant women increased
Mean Length of Hospital Stay

Infants treated with outpatient methadone (UVM Children’s Hospital)
UVM Children’s Hospital
Breastfeeding at discharge

Rate

Opioid-exposed infants
All Infants at UVMHC
• Average length of treatment: 3.2 months (2014)

• No infant deaths from methadone overdose

• Developmental outcomes on 166 children assessed at 7-14 months with the Bayley III scale mean percentiles > 50th%

• From 2000 to June 4th, 2015 there were 13 deaths / 1278 opioid-exposed infants (deaths < 2 years of age)

• Shared sleeping: 7

• Motor vehicle accidents: 2

• Remainder (1 each): SIDS, congenital heart malformation, extreme prematurity, abusive head trauma
Vermont Experience: Overall

- ChARM Team: Children and Recovering Mothers
- Monthly multidisciplinary meetings with multiple agencies: impaneled
- High risk factors:
  - Increased distance to treatment center
  - Discontinuation of methadone / buprenorphine
  - Actively using partner
  - Abusive relationship with partner
- Women respond well to positive interactions with health care providers
Summary of NOWS

- NOWS is increasing in US with increase in healthcare costs.
- Behind every case of NOWS, there is a mother suffering from the disease of addiction – this is where efforts need to be the greatest.
- Several factors can contribute to NOWS severity.
- Many scoring tools – none are truly validated.
- Non-pharmacologic treatment can affect NOWS.
- AAP endorses morphine or methadone for NOWS.
- Developmental / behavioral outcomes are overall not affected by opioid-exposure in utero on its own, unlike alcohol exposure.
- UVM has program which decreases length of stay and healthcare costs safely and effectively.
The health of the baby depends upon the mother’s health.
I would like to thank the infants and families I have had the pleasure of caring for – I continue to learn from them daily.