Understanding Neonatal Abstinence Syndrome for the General Pediatrician

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August 23, 2017

Providers’ Clinical Support System – Opioid Therapies (PCSSO)

- Grant funded by SAMHSA
- Coalition of professional organizations
- Overarching goal: To offer evidence-based trainings on the safe and effective prescribing of opioid medications in the treatment of pain and/or opioid addiction.
- AAP = 2 Webinars per grant year (6 total)
- www.pcss-o.org

CME

CME credit is available for this Webinar upon completion of an evaluation.

More information will be provided near the end of this presentation.

Educational Objectives

At the conclusion of this activity participants should be able to:
- summarize epidemiology and population health consequences of opioid use in the US, including NAS.
- review treatment of NAS, including non-pharmacologic interventions.
- describe the need for long-term outcome follow-up of infants exposed to opioids in-utero and those who receive pharmacologic treatment for NAS.

1827 Morphine marketed by Merck
- Pain relief
- Treatment of ‘opium addiction’
- Treatment of ‘alcoholism’


Additional Source: Hendree Jones, PhD

- 1827 Morphine marketed by Merck
- Pain relief
- Treatment of ‘opium addiction’
- Treatment of ‘alcoholism’
1874 Diacetylmorphine discovered
1898 Bayer pharmaceutical marketed under name Heroin
The marketing campaign
"safe, non-addictive" substitute for morphine
1906 American Medical Association approved Heroin for general use and recommended that it be used in place of morphine.


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 risk, risk of addiction and the potential to be abused.” Results in a $600M settlement.

2000+
• Rapid expansion of opioid use in the US


Opioid Pain Reliever Prescribing
Annual prescribing rate

Opioid Prescribing, US 2015
Opioids

- Prescriptions, recently decreased but:
  - 3-fold higher in 2015 compared to 1999
  - 4-fold higher than Europe
- More deaths than car accidents
- Rising deaths from heroin and synthetic opioids

Source: Centers for Disease Control and Prevention

What about Other Drugs?

- Illicit drug use in pregnancy (2015)
  - 7.4% - pregnant women 18 to 25 years old
  - 4.7% - 15-44 years (less than non-pregnant 12.5%)
- Legal drugs in pregnancy
  - 13.6% smoke cigarettes (11.4% in 2014)
  - 9.3% use alcohol (8.8% in 2014)
- 440,000 infants exposed to illicit drugs and alcohol per year
  - Only 5% detected at birth


Maternal Drug Use

- Commonly occurs with other substances
  - Among pregnant women misusing opioids in last year (compared to those who did not), in the last month:
    - 22.9% used marijuana (versus 2.6%)
    - 23.9% used alcohol (versus 8.1%)
    - 43.5% used tobacco (versus 14.5%)

Young NL, et al. Substance-Exposed Infants: Data Responses to the Problem. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009.

Opioid Agonist Therapies

- Buprenorphine and methadone
  - Approved to treat opioid use disorder in pregnancy
  - Mother: Decreased risk of overdose death, relapse, HCV, HIV
  - Baby: More likely to go to term, higher birthweights
  - Risk of NAS
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

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 opioid-exposed population
  - Currently poly-substance exposure is the norm
  - Finnegan paper = average LOS was 6 days . . .

Incidence of NAS in the US, 2000-2012

Neonatal Abstinence Syndrome in Rural vs. Urban Communities
Mean LOS and Hospital Charges for NAS, 2009-2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean LOS (day)</th>
<th>Mean Charges* (2012 US$)</th>
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</thead>
<tbody>
<tr>
<td>2009</td>
<td>22.7</td>
<td>$75,700</td>
</tr>
<tr>
<td>2010</td>
<td>22.9</td>
<td>$80,500</td>
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<tr>
<td>2011</td>
<td>22.8</td>
<td>$87,700</td>
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<tr>
<td>2012</td>
<td>23.0</td>
<td>$93,400</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>Year</th>
<th>Medicaid*</th>
<th>Private Payer*</th>
<th>Self Pay*</th>
<th>Other Payer*</th>
<th>Total Charges*</th>
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<tbody>
<tr>
<td>2009</td>
<td>$560M</td>
<td>$870M</td>
<td>$900M</td>
<td>$14M</td>
<td>$730M</td>
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<td>2010</td>
<td>$600M</td>
<td>$870M</td>
<td>$900M</td>
<td>$30M</td>
<td>$900M</td>
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<tr>
<td>2011</td>
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<td>$870M</td>
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<td>$900M</td>
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*p<0.001
**NAS Treatment**

- Goal of treatment to “control” withdrawal, minimizing complications (e.g. seizure)
- Non-pharmacologic intervention (e.g. environmental controls)
- Pharmacotherapy with an opioid (morphine, methadone) and slowing decreasing dose

**Hospital Variability**

- There remain significant inter and intra-hospital variation in treatment and outcomes for NAS
- Recent study of US children’s hospitals:
  - Only 5/14 used the same pharmacotherapy >80% of the time
  - Two-fold differences in risk-adjusted length of stay
- Large international quality improvement collaborative of 199 hospitals
  - 44.8% had a policy to standardize scoring
  - 48.6% had a policy on breastfeeding a substance-exposed infant
  - 68.0% had a policy on pharmacologic treatment of NAS

**Standardizing Care Works**

- Ohio perinatal collaborative, multicenter cohort
  - Protocol driven weans vs. no protocol - with shorter LOT (17.7 vs. 32.1 days, p=0.001)
- Vermont Oxford Network NAS collaborative 2013-2015
  - Participating hospitals, care standardized by protocol/policy development
  - Shortened LOT (16 → 15, p=0.02) and LOS (21 → 19, p=0.002)
  - Hospitals with protocols/policies on infant scoring lowest LOS ~3.1 days (95%CI –4.9, –1.4)

**Rooming In**

- Rooming in = creating an environment where moms/babies can stay together
- Culture differences between NICU, newborn nursery general inpatient wards?
  - NICU environment conducive to withdrawal?
    - Loud
    - Open bay
    - Bright

**Dartmouth as a Model**

1. RN scoring training/reliability
2. Family interviews
3. Baby-centered scoring
4. Prenatal education
5. Parent symptom diary
6. “Cuddlers”
7. Full room in pilot
8. “Cuddlers”
9. Full room in pilot
10. Addiction training
11. Transfers

**Dartmouth**

- % Opioid-exposed Newborns Receiving Morphine
- % Opioid-exposed Newborns Receiving Adjunctive Agents

N = opioid-exposed infants per year

Source: Bonny Whalen, MD and Alison Holmes, MD
Breastfeeding

- Breastfeeding safe and effective
  - Promotes bonding
  - Very little MAT medications in breastmilk
  - Reduces LOS for NAS

- American Breastfeeding Medicine
  - Appropriate: >90 days in treatment
  - Inappropriate: Active illicit use
  - Maybe: >30 days in treatment

After Discharge from Hospital?

- Recent focus on reducing LOS
  - Infants with NAS 2x as likely to be readmitted in 30 days than uncomplicated term infants
    - Short LOS increase risk or readmission

- Many hospitals discharging home on medications
  - Shorter LOS - 11 (IQR 7-18) vs. 23 (IQR 14-35)
  - Longer LOT - 59 days (IQR 38-90) vs. 19 days (IQR 10-31)
  - Use of ED > in first 6 months (aOR 1.46, 95% CI 1.02-2.09)

Hepatitis C Prevalence Among Pregnant Women

- Per 1,000 Live Births

<table>
<thead>
<tr>
<th>Year</th>
<th>Tennessee</th>
<th>US</th>
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<tbody>
<tr>
<td>2009</td>
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<td>5.4</td>
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<tr>
<td>2012</td>
<td>2.6</td>
<td>7.0</td>
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<tr>
<td>2013</td>
<td>3.0</td>
<td>7.8</td>
</tr>
<tr>
<td>2014</td>
<td>3.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Hepatitis C Prevalence Among Pregnant Women, US 2014

NAS Summary - Priorities

- Focus on scoring
- Focus on non-pharm care and rooming-in
- Be consistent (i.e. adhere to a protocol)
- Look beyond the baby
  - Talk to OB
  - Work on transition home
Long-Term Outcomes

- Maternal drug use does not occur in isolation
  - Poor health
  - Poor nutrition (food insecurity)
  - Poor prenatal care
  - Social stress
  - Associated with poor obstetric outcomes
  - Each common factors which could impact neurodevelopmental outcomes

Maternal Drug Use

- Maternal drug use does not occur in isolation
  - Poor health
  - Poor nutrition (food insecurity)
  - Poor prenatal care
  - Social stress
  - Associated with poor obstetric outcomes
  - Each common factors which could impact neurodevelopmental outcomes

Alcohol Exposure

- Alcohol is a frequently un- or under-recognized exposure
- Prenatal alcohol use is the chief preventable cause of developmental delay in children
- Alcohol use is common, especially among mothers with substance use disorder
- How do long-term developmental studies account for it?

Mechanisms

- Drug exposure can impact development through several mechanisms
  - Crossing placenta (most do) and have direct effect on fetus
  - Direct action on uterus or placenta  
    - e.g. Alteration of placental blood flow
  - Secondary effects of fetus from maternal drug use  
    - e.g. Maternal stress hormones

Drug effects do not appear in isolation

- Polysubstance use
- Maternal clinical comorbidities
- Maternal psychiatric conditions

What about later in life?

- Large cohort from New South Wales, Australia
  - Infants followed from 2000-2011
  - Reasons for care (compared to other infants)
    - Anxiety (aOR 3.77; 3.09-4.61)
    - Behavioral/emotional d/o (aOR 3.35; 3.02-3.72)
    - Stabismus (aOR 3.13; 2.72-3.59) and nystagmus (aOR 4.61; 3.43-6.20)
    - Drug poisoning (aOR 1.39; 1.17-1.66)
    - Maltreatment (aOR 3.38; 2.87-4.26)
    - Assault (aOR 4.20; 3.58-4.93)
Neurodevelopmental Outcomes

Behavior

- Rosen (prospective cohort)
  - Methadone maintenance - 61 infants from birth to 36 months (36% loss)
  - Comparison – 32 infants matched on races, SES, sex, birth weight and gestational age (28% loss)
  - Methadone group, more likely smokers, polysubstance users (15% heavy drinkers)
  - 36 months – no growth differences, but higher incidence of smaller head circumference among methadone-exposed
  - Increased rates of strabismus/nystagmus, otitis media

- Rosen (prospective cohort)
  - 36 mo: Hypertonia, poor fine motor, delays in attaining developmental milestones, poor language development
  - 84 mo: “generally healthy,” higher prevalence:
    - Abnormal fine/gross motor coordination
    - Poor balance
    - Hyperactivity
    - Decreased attention
    - Speech/language delays

- Rosen (prospective cohort)
  - “no uniform long-term effects”
  - “minor neurologic abnormalities”
  - Lower scores on developmental evaluations
  - Differences smaller as infants aged
  - Factors noted to improve outcomes at 36 months
    - Maternal education and family stability

Cognition

- Lifschitz (prospective cohort)
  - 25 heroin; 26 methadone maintenance; 41 with no documented substance use
  - Initial findings
    - Mean head circumference lower (heroin/MMT)
  - Long-term
    - Low-average to mild intellectual disability (heroin/MMT)
    - Adjusted analysis: Amount of prenatal care, prenatal risk, home environment all predictive of intellectual outcome and NOT drug use

Additional Studies

- NAS vs. controls, 6 months (McGlonle 2015)
  - Developmental delay, visual difficulties
  - Analyses controlled for EtOH and smoking

- Norway, 50k infants, ~900 opioid pain reliever-exposed (Skovlund 2017)
  - No language differences

- Opioid-exposed vs. Control, n=23 (Walhovd 2015)
  - MRI no structural differences
  - Differences in visual acuity
Summary of Outcomes

<table>
<thead>
<tr>
<th>Short-term Effects/Birth Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal growth</td>
<td>Effect</td>
</tr>
<tr>
<td>Anomalies</td>
<td>No effect</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Strong effect</td>
</tr>
<tr>
<td>Neurobehavior</td>
<td>Effect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-term Outcome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>No effect</td>
</tr>
<tr>
<td>Behavior</td>
<td>Effect</td>
</tr>
<tr>
<td>Cognition</td>
<td>No consensus on effect</td>
</tr>
<tr>
<td>Language</td>
<td>Limited or no data</td>
</tr>
<tr>
<td>Achievement</td>
<td>Limited or no data</td>
</tr>
</tbody>
</table>


Substance Use as a Symptom

- More than ¾ women in treatment for substance use disorder report history of trauma or abuse
- Among inmates, physical abuse, sexual abuse, foster care involvement and caretakers who use drugs increase risk of substance use
- Trauma common, substance use often coping

Adverse Childhood Experiences

When you were growing up, during your first 18 years of life, did you experience:

- Physical abuse
- Emotional abuse
- Sexual abuse
- Domestic violence (mother treated violently)
- Substance abuse in home
- Mental illness in parent
- Lost parent due to separation or divorce
- Household member in jail

ACES and Risk of Illegal Drug Use

- Longitudinal studies of opioid exposure
  - Inconsistent findings on development
  - Developmental scores tend to be lower
    - Differences disappear when medical/environmental controls applied
  - Studies small N, often confounded
Pediatrician Take Away?

- It appears that there are not substantial issues with development
- How can we modify developmental outcomes?
  - Avoid long weans, especially with phenobarbital
  - Helping family engage in treatment
  - Discharge plan
    - Child welfare when appropriate
    - Early intervention services
    - Communication/follow-up plans

AAP Policy Statement

- Public Health vs. Punitive Response
  - Focus on prevention (improving access to contraception)
  - Universal screening for alcohol and drug use in women of childbearing age
  - Informed consent for drug testing
  - Improve access to comprehensive addiction and prenatal access
  - Improved funding for child welfare systems

More to come …

- Update to 2012 AAP policy statement on drug withdrawal.

Q & A

- Please use the chat box to submit a question for the speakers.
- Obtaining CME
  - After the event, you will receive a link taking you to an evaluation. Upon completion, you will be emailed your CME certification.
  - The American Academy of Pediatrics (AAP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.
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  - This activity is accredited for 1.0 National Association of Pediatric Nurse Practitioners (NAPNAP) CE contact hours of which 0 contain pharmacology (Rx), (0 related to psychopharmacology) (0 related to controlled substances), (0 related to pain management) (0 related to infection control) (0 related to nutrition), and (0 related to emergency preparedness/terrorism) of which 0 are practice-based learning and improvement (PBLI) activity. This activity is endorsed by NAPNAP.

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PCSS-O Colleague Support Program and Listserv

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.
- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.
- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.
- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: www.pcss-o.org/colleague-support

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org

PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with Addiction Technology Transfer Center (ATTC), American Academy of Neurology (AAN), American Academy of Pain Medicine (AAPM), American Academy of Pediatrics (AAP), American College of Physicians (ACP), American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), International Nurses Society on Addictions (INSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: www.pcss-o.org
For questions email: pcss-o@aaap.org
Twitter: @PCSSProjects

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