Substance Use Disorder in Pregnancy: Opioids

Project RESPECT
Kelley Saia, MD
Outline

• Opioid Epidemic: Heroin and the scope of the problem
• Substance Use Disorder / Opioid Addiction
• Equation for Addiction

• Project RESPECT: the treatment program
  – Methadone
  – Buprenorphine
Heroin
leading cause of death ages 25-49

Phillip Seymour Hoffman. 1967-2014
Opioids in US
2013: National Institute on Drug Abuse

WHO 2013

2 million Americans addicted to prescription opioids
Substance Abuse and Mental Health Services Administration 2011 report

- Boston ranked first in ER treatment for heroin overdoses
- 4 times the national rate

The Boston region includes Suffolk, Middlesex, Norfolk, Plymouth and Essex counties plus two New Hampshire counties
Addiction Treatment
Opioid maintenance therapy reduces opioid-related mortality by 70%

Overdose Prevention
Since 2007, MA Narcan Program reversed over 3,200 overdoses
Understanding Addiction

• American Medical Association
• Substance Use Disorder: DSM V
• Definition of addiction
American Medical Association 1956

The Disease of Addiction

• Predictable and progressive
• Primary
• Permanent
• Terminal

Solutions Outpatient Services; Texas Department of State Health Services
DSM V: Substance Use Disorder: patterns of symptoms resulting from use of a substance which the individual continues to take, despite experiencing problems as a result

- Taking the substance in **larger amounts** or for longer than the you meant to
- Wanting to **cut down** or stop using the substance but not managing to
- Spending a lot of time **getting, using, or recovering** from use of the substance
- **Cravings** and urges to use the substance
- Not managing to do what you should at **work, home or school**, because of substance use
- Continuing to use, even when it **causes problems** in relationships
- Giving up important **social, occupational or recreational activities** because of substance use
- Using substances again and again, even when it puts the you in **danger**
- Continuing to use, even when the you know you have a physical or psychological problem that could have been caused or made worse by the substance
- Needing more of the substance to get the effect you want (**tolerance**)  
- Development of **withdrawal symptoms**, which can be relieved by taking more of the substance
Addiction: definition

• The state in which a person engages in compulsive behavior and pursuit of a reward despite the hazards or consequences
• The compulsion is rewarded and reinforced by neurobiological pathways
• Ultimately: loss of control in limiting the intake/exposure
Equation for Opioid Addiction

Drug availability

Neurobiology

Genetics

Environmental
**Historical**

1830: Stickney and Poor’s marketed *Paragoric*

46% ETOH + one and three-sixteenth "grains of opium per ounce"

Dosage chart for newborns, children and adults

1870: Bayer synthesized and marketed as analgesic

Not addictive

To treat Morphine addiction
FDA NEWS RELEASE: October 25, 2013

Zohydro ER

• Extended-release/long-acting (ER/LA) opioid analgesics

• Manufactured by San Diego-based Zogenix, Inc.
Drug Availability: Prescription Opioid Statistics in US

Number of Opioid Prescriptions (in millions)
1991, 2010

- 1991: 76 million
- 2010: 206 million
Diacetylmorphine: Heroin

- 2010: Afghanistan supplied 80% of the world's opium
- US heroin supply from Mexico, Columbia
40%-60% attributable to genetic vulnerability

- P450 2A6: protective against nicotine addiction
- P450 2D6: protective against codeine abuse
- GABA type A: predisposes to ETOH abuse
Equation of Opioid Addiction

- Neurobiology
- Genetics
- Environment
- Drug availability
Neurobiology of Addiction

• Limbic System: emotion, memory, impulse
  – 8 main regions: including amygdala, basal ganglia, hippocampus and olfactory cortex
  – g-protein coupled opioid receptors (μ, k, delta)

• Prefrontal Cortex: center of executive function
  – 3 main regions: decision making, execution of actions and reward pathways
Dopamine reward pathways

• Drugs of abuse increase the extracellular dopamine in Limbic regions
• 5-10 fold sustained increases in dopamine release
• Reuptake inhibitors:
  – Cocaine, amphetamines, methamphetamines, ecstasy: dopamine
• Alterations in receptor function
  – Opioids, nicotine, alcohol and marijuana
Chronic use changes Dopamine receptor

- D2 receptors: five types of receptors that bind dopamine in the brain

- D2 receptors in striatum shows up as bright red and yellow
A. Non Dependent

B. Dependent

C. Dependent: Stress-induced relapse

D. Non Dependent

E. Dependent

F. Extracellular level
Equation of Opioid Addiction

- Drug availability
- Neurobiology
- Genetics
- Environment
Trauma

- **178 women in treatment for Substance Use Disorder**
  - 84% reported history of childhood sexual abuse or neglect

- Adolescents who had experienced physical or sexual abuse/assault were **three times more likely** to report past or current substance abuse

- **Over 70% of adolescents** receiving treatment for substance abuse reported a history of trauma exposure


*National Survey of Adolescents 2003*
Environment

Social factors

• Low socioeconomic status
• Unhealthy or Unstable support network
• Housing instability
• High drug availability

New stressors
Project RESPECT: Substance Use Disorder Treatment in Pregnancy

- Recovery
- Empowerment
- Social services
- Prenatal Care
- Education
- Community
- Treatment

- 150 patients annually
  - 2006-2010: > 600 women
  - 2010: increased volume by 30%

- 60% Methadone
  - Average dose 68mg/day

- 40% Buprenorphine
  - Average dose 12mg/day
Project RESPECT: the program

**Out-patient team**
- Psychiatrist
- LICSW
- Addiction Psychiatry NP
- Clinic Coordinator
- Medical Assistant
- 3 OB/Addiction Providers

**In-patient team**
- Labor and delivery: RNs, Residents, OB Providers
- Postpartum: RNs, Social Work, Lactation, PT/OT, Psychiatry, Pediatric Newborn Nursery Team
- 4E: RNs, Social Work, PT/OT, Pediatric teams
How do women enter RESPECT?

- Self referral, provider referral, transfer from a detox program
Opioid Maintenance Therapy

Methadone

Buprenorphine
Pregnant Physiology: Maintenance Dose

- **Total blood volume**: 45% increase by 28wks

- **Cardiac Function**:
  - HR 10-15 bpm
  - CO 30-50% increase by 2nd

- **GFR increases**

- **Terminal half-life decreases** in 2nd and 3rd trimesters

- **Lower trough levels**

- **Withdrawal symptoms**
Opioid Maintenance in Pregnancy

- Dosing changes
- Split dosing
Maternal Dose and NAS Severity

NO CORRELATION
Detoxification

- **Zuspan 1975**: cortisol levels
  - N=1

- **Rementeria 1973**: 5 fold increase stillbirth
  - High risk pregnancies
Opioid Detox. Studies in Pregnancy

• **Maas** et al: 1990: 2-8 wks outpt detox: 59 women
  • 17 completed detox, no relapse

• **Dash**i et al: 1998 12-day MTD detox: 34 women
  • 59% completed, no relapse (out pt pnv, did not do urines)

• **Luty** et al: 2003: 101 women, only 50 women booked for PNC
  • 1 of 50 “drug free” at delivery

• **Jones** et al: 2008: treatment retention, PNVs, hospital delivery
Pregnancy: Induction of Maintenance Therapy

- Goal is to reach the dose just high enough to stop use and block cravings
- Management of dose should be individualized and based on patients’ symptoms
- Dose adjustments are often necessary with advancing gestational age based on pregnant physiology (see next slide)

  - Split dosing, when available, is ideal in pregnancy to meet the accelerated metabolic clearance of pregnancy

  - Split dosing with methadone can help to avoid peak dose sedation and pre-dose withdrawal symptoms
Managing Maintenance Therapy through Pregnancy

**Methadone**
- Risk of Prolonged QTc Syndrome:
  - Obtain baseline EKG
  - Repeat with dose increase > 100mg
  - May be mitigated with split dosing

**Buprenorphine**
- Evaluation of liver function
  - Obtain Baseline LFTs: follow through pregnancy, may require dose adjustments
  - Elevated LFTs may complicate diagnosis of pre-eclampsia >20wks
  - Monotherapy: higher risk of diversion
Opioid Maintenance: Improved outcomes

• Maternal:
  – Relapse prevention
  – Reduces polysubstance use
  – HBV, HCV, HIV
  – Increases engagement with prenatal care/health care

• Neonatal:
  – Decreases preterm delivery and IUGR
  – Decreases NICU admissions
  – Decreases morbidity/mortality
• Fatigue / Stress
• Physical / Emotional Changes
• Breastfeeding
• Postpartum/ Postoperative Pain
• NAS Anxiety
• DCF Anxiety
• Family Stressors
• Demands of Recovery Program

• Postpartum Visit QI
• RESPECT team rounding 4E
• 4E Drop-in Support Group
• Social Work Communication
Managing Maintenance Therapy through labor and Delivery

- Labor Pain: Epidural only!
  - Commonly used intrapartum opioid agonist/antagonists will precipitate withdrawal

- Maintain Dose Through Labor and Delivery
  - For scheduled or unscheduled C-sections, continue maintenance therapy at same dose into the postpartum period

- Post C-Section Pain: use IV NSAIDS and Opioids as needed
  - Women on maintenance therapy will require higher doses than opioid naïve women to treat post-operative pain (Meyer et al 2007, Jones et al 2009)

- Tapering Post-Partum Dose: any adjustments should be individualized
  - Rapid postpartum taper is not recommended
  - Relapse prevention, support and stabilization should be the goal
Breastfeeding Benefits in General Population

- Benefits for all mother-infant pairs:
  - Decreased risk of SIDS, diabetes, and obesity for children
  - Decreases risk of breast and ovarian cancer for women
  - Improved infant cognitive development
  - Improved mother-infant bonding
  - Financial benefits

- Additional benefits for preterm infants:
  - 50% reduction in necrotizing enterocolitis
  - Better feeding tolerance and attainment of full enteral feedings
  - Decreased rates of late onset sepsis
  - Improved developmental outcomes

AAP 2012
Opioid Use Disorder and Breastfeeding

- The transfer of methadone and into human milk is minimal
- Concentrations of methadone in breast milk are unrelated to maternal doses and are particularly low in infant plasma, therefore unlikely to cause any adverse effects on the infant
- Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
- The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- Both are considered Category L3

Breastfeeding and NAS

- Benefits of breastfeeding for newborns with NAS
  - 30% decrease the development of NAS
  - 50% decrease in neonatal hospital stay
  - Improved mother-infant bonding
  - Positive reinforcement for maternal recovery

Breast feeding

- Breastfeeding is recommended for women with HCV infection
  - Unless she develops cracked or bleeding nipples
    - Recommend to pump/dump until healed

- **Contraindications** to breastfeeding
  - Maternal HIV infection
  - Current maternal substance use
    - mother currently under the influence of illicit substance
  - Recent heavy marijuana use
    - lipophilic, concentration in breast milk
Project RESPECT Team

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• Michelle Sia, DO
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617-414-4165
References

- Finnegan L. Treatment Issues For Opioid-dependent Women During The Perinatal Period. *Journal Of Psychoactive Drugs* 1991;23:191-201
Thank you!
Maternal Opioid Treatment Human Experimental Research (MOTHER)
NEJM 12/2010

- Double-blind, double-dummy, flexible-dosing, parallel-group clinical trial
- Comparing MMT and Buprenorphine

- 73 MMT
- 58 Buprenorphine

- Shorter Hospital Stay (10 days vs. 17 days)
- Lower Mean Dose of Morphine (1.1mg vs 10.4mg)
- Shorter Duration of Treatment (4 days vs. 9 days)
Table I. Maternal Characteristics by Prenatal Opioid Agonist Treatment for 435 Pregnancies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Opioid Agonist Treatment (N=103)</th>
<th>Buprenorphine (N=82)</th>
<th>Methadone (N=245)</th>
<th>Buprenorphine and Methadone (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age, Years</td>
<td>30.2 ± 6.4</td>
<td>28.1 ± 5.1</td>
<td>27.7 ± 5.1</td>
<td>27.2 ± 3.3</td>
</tr>
<tr>
<td>No Prenatal Care</td>
<td>16 (15.6)</td>
<td>0 (0)</td>
<td>3 (1.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gestational Age at Presentation for Care, Weeks</td>
<td>16.8 ± 8.8</td>
<td>16.4 ± 8.9</td>
<td>17.2 ± 8.9</td>
<td>118 ± 8.6</td>
</tr>
<tr>
<td>Number of Prenatal Care Visits</td>
<td>6.5 ± 5.3</td>
<td>11.5 ± 4.7</td>
<td>8.7 ± 4.3</td>
<td>116 ± 2.2</td>
</tr>
<tr>
<td>Initial Daily Dose of Opioid Agonist Therapy (mg)</td>
<td>-</td>
<td>12.0 ± 6.5</td>
<td>68.3 ± 37.4</td>
<td>12.0 ± 4.0</td>
</tr>
<tr>
<td>Stopped Agonist Therapy During Pregnancy</td>
<td>-</td>
<td>2 (2.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Daily Dose of Opioid Agonist Therapy at Delivery (mg)</td>
<td>-</td>
<td>15.1 ± 7.5</td>
<td>89.3 ± 41.7</td>
<td>77.0 ± 28.9</td>
</tr>
<tr>
<td>Prescribed Psychiatric Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>7 (6.8)</td>
<td>14 (17.1)</td>
<td>38 (15.5)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 (2.9)</td>
<td>14 (17.1)</td>
<td>51 (20.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>3 (2.9)</td>
<td>1 (1.2)</td>
<td>18 (7.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.9)</td>
<td>9 (11.0)</td>
<td>15 (6.1)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>≥1 Urine Screen</td>
<td>58 (56.3)</td>
<td>78 (95.1)</td>
<td>233 (95.1)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>≥1 Positive Urine Screen</td>
<td>42 (72.4)</td>
<td>31 (39.7)</td>
<td>123 (52.8)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Unexposed (N=103)</td>
<td>Buprenorphine (N=82)</td>
<td>Methadone (N=245)</td>
<td>Buprenorphine &amp; Methadone (N=5)</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
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<tr>
<td>Pharmacologically Treated for NAS</td>
<td>6 (5.8)</td>
<td>57 (69.5)</td>
<td>221 (90.2)</td>
<td>4 (80.0)</td>
</tr>
<tr>
<td>Length of Hospitalization, Days</td>
<td>7.3 ± 12.1</td>
<td>16.0 ± 10.5</td>
<td>24.8 ± 11.3</td>
<td>21.4 ± 9.1</td>
</tr>
<tr>
<td>Age at NAS Treatment Initiation, Days</td>
<td>1.7 ± 1.2</td>
<td>2.4 ± 1.5</td>
<td>2.2 ± 2.3</td>
<td>1.8 ± 1.0</td>
</tr>
<tr>
<td>First-line NAS Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine DTo</td>
<td>5 (83.3)</td>
<td>43 (75.4)</td>
<td>103 (46.6)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td></td>
<td>1 (16.7)</td>
<td>14 (24.6)</td>
<td>118 (53.4)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>Total Morphine Used to Treat NAS, Mg per Kg Birth Weight**</td>
<td>3.1 ± 2.7</td>
<td>4.4 ± 4.1</td>
<td>8.8 ± 7.8</td>
<td>9.2 ± 4.0</td>
</tr>
<tr>
<td>Additional NAS Treatment with Phenobarbital or Clonidine</td>
<td>1 (16.7)</td>
<td>7 (12.3)</td>
<td>66 (29.9)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Length of NAS Treatment, Days</td>
<td>17.2 ± 12.2</td>
<td>14.3 ± 7.0</td>
<td>20.3 ± 9.5</td>
<td>20.0 ± 7.0</td>
</tr>
<tr>
<td>Peak Finnegan Score Among Neonates Treated for NAS</td>
<td>11.8 ± 3.8</td>
<td>11.1 ± 2.1</td>
<td>12.9 ± 3.0</td>
<td>13.3 ± 3.0</td>
</tr>
<tr>
<td>Gestational Age at Birth, Weeks</td>
<td>38.0 ± 3.1</td>
<td>39.2 ± 1.9</td>
<td>38.1 ± 2.4</td>
<td>38.5 ± 2.0</td>
</tr>
<tr>
<td>Preterm birth, &lt;37 Weeks</td>
<td>17 (22.7)</td>
<td>6 (7.3)</td>
<td>51 (20.8)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td>Birth Weight, Grams</td>
<td>2919.3 ± 705.5</td>
<td>3146.1 ± 558.9</td>
<td>2792.8 ± 610.4</td>
<td>2968.0 ± 359.5</td>
</tr>
</tbody>
</table>