Relevant Disclosures

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Stephen Patrick has no financial relationships or affiliations to disclose.
History

- History
- Trends in Opioid Use
- Substance Exposure in Pregnancy
- NAS
- Federal and State Policy
Happel TJ. Morphinism in its relation to the sexual functions and appetite and its effects on the offspring of the users of the drug. Tr M Soc Tennessee. 1892;162–179
The quantity of opium used in the United States has largely and rapidly increased. In 1859 the amount imported was about 72000 pounds, in 1880, 372000 pounds, in 1890, about a half million pounds. The legitimate demands of medicine would call for an increase in quantity commensurate with the increase in population; but see the contrast:—

The difference between the legitimate demands of medicine and the actual amount used shows how much approximately is consumed by opium eaters. This fact no doubt largely accounts for the rapid increase in the number of cases of insanity, idiocy, and imbecility in the present generation.
CASE V. Mrs. — used morphine for years, and at the time of the birth of her third child was consuming eight or ten grains a day. In 1884 she gave birth to a well nourished and apparently perfectly developed boy, weight seven or eight pounds. Within twenty-four hours the child began to grow restless and nervous. In the next twenty-four hours this nervousness increased, and the child frequently became cyanotic; on the third day all the symptoms grew worse, the cyanotic condition continuing almost all the time; on the fourth day the child died. Not knowing anything provingly
Happel TJ. Morphinism in its relation to the sexual functions and appetite and its effects on the offspring of the users of the drug. Tr M Soc Tennessee. 1892;162–179
- 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.


Additional Source: Hendree Jones, PhD
PROGNOSTIC VALUE OF IMMUNOLOGIC MARKERS IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

To the Editor: The letter from Dr. Bitran\(^1\) has raised an important but as yet unsettled question about prognostic factors in acute lymphoblastic leukemia in adults. On the basis of experience with 13 patients, Dr. Bitran suggested that adults with T-cell disease could have a limited survival and a lower rate of remission than those with B-cell disease. From January, 1974, to June, 1979, we studied 42 consecutive adults (more than 12 years old) with acute lymphoblastic leukemia for sheep-erythrocyte rosette formation and surface immunoglobulins. Patients were classified as having T-cell disease if they had more than 40 per cent of marrow blast cells forming E-rosettes, or B-cell disease if they were positive for surface immunoglobulins. Details on the techniques have been reported elsewhere.\(^2\) There were 31 patients with null-cell leukemia, eight with T-cell leukemia, and four with B-cell leukemia. All patients were treated with vincristine (1.6 mg per square meter of body-surface area each week in five to six doses), daunorubicin (40 mg per square meter in two to three doses), and prednisone (40 mg per square meter each week in two to three doses).


PROGNOSTIC VALUE OF IMMUNOLOGIC MARKERS IN ADULTS WITH ACUTE LEUKEMIA: BASED ON EXPERIENCE WITH 13 SUGGESTED THAT ADULTS WITH T-CELL DISEASE COULD HAVE A LIMITED SURVIVAL AND A LOWER RATE OF REMISSION THAN THOSE WITH B-CELL DISEASE. FROM JANUARY, 1974, TO JUNE, 1979, WE STUDIED 42 B-CELL DISEASE. FROM JANUARY, 1974, TO JUNE, 1979, WE STUDIED 42 CONSECUTIVE ADULTS (MORE THAN 12 YEARS OLD) WITH ACUTE LYMPHOBLASTIC LEUKEMIA FOR SHEEP-ERYTHROCYTE ROSETTE FORMATION AND SURFACE IMMUNOGLOBULINS. PATIENTS WERE CLASSIFIED AS HAVING T-CELL DISEASE IF THEY HAD MORE THAN 40 PER CENT OF MARROW BLAST CELLS FORMING E-ROSETTES, OR B-CELL DISEASE IF THEY WERE POSITIVE FOR SURFACE IMMUNOGLOBULINS. DETAILS ON THE TECHNIQUES HAVE BEEN REPORTED ELSEWHERE.2 THERE WERE 31 PATIENTS WITH NULL-CELL LEUKEMIA, EIGHT WITH T-CELL LEUKEMIA, AND FOUR WITH B-CELL LEUKEMIA. ALL PATIENTS WERE TREATED WITH VINCRISTINE (1.6 MG PER SQUARE METER OF BODY-SURFACE AREA EACH WEEK IN FIVE TO SIX DOSES), DAUNORUBICIN (40 MG PER SQUARE METER IN TWO TO THREE DOSES), AND PREDNISONE (40 MG PER SQUARE Meter).
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MEDICAL CENTER

Number and Type of Citations of the 1980 Letter, According to Year.

1996 • American Pain Society “Pain as the 5th Vital Sign Campaign”

1998 • Federation of State Medical Boards published "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."

2003 • The New York Times reports tripling of young adults (18-25) abusing opioid pain relievers. DEA and FDA create task force to crack down on internet sales of opioids.

2007 • Maker of OxyContin, Purdue Pharma, plead guilty to “criminal charges that they misled regulators, doctors and patients about the drug’s risk of addiction and its potential to be abused.” Results in a $600M settlement.

2000+ • Rapid expansion of opioid use in the US

Trends in Opioid Use

1. History
2. Trends in Opioid Use
3. Substance Exposure in Pregnancy
4. NAS
5. Federal and State Policy

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Opioid Pain Reliever Sales

Centers for Disease Control and Prevention

@stephenwpatrick
Opioid Pain Reliever Prescribing


@stephenwpatrick
Opioid Prescribing, US 2015

Opioid Prescription Rates by County—TN, 2007

Source: Michael Warren, MD, MPH – Tennessee DOH

Data source: Tennessee Department of Health; Controlled Substance Monitoring Database.
Opioid Prescription Rates by County—TN, 2008

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Opioid Prescription Rates by County—TN, 2010

Data source: Tennessee Department of Health; Controlled Substance Monitoring Database.

Source: Michael Warren, MD, MPH – Tennessee DOH
Opioid Prescription Rates by County—TN, 2011

Source: Michael Warren, MD, MPH – Tennessee DOH
Data source: Tennessee Department of Health; Controlled Substance Monitoring Database.
Opioid Overdoses, US 2000-2015

Deaths per 100,000 population

- Any Opioid
- Commonly Prescribed Opioids (Natural & Semi-Synthetic Opioids and Methadone)
- Heroin
- Other Synthetic Opioids (e.g., fentanyl, tramadol)

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Death rate per 100,000

- 0-4
- 4.1-8
- 8.1-12
- 12.1-16
- 16.1-20
- 20+

2002 | US: 23,518 deaths | 8.2 per 100,000

Credit: Scott Wexelblatt, MD
Opioids

• Prescriptions grew 4-fold over last decade
• More deaths than car accidents
• In 2012, enough OPR were prescribed to give every adult in the US one prescription
• Rising deaths from heroin and synthetic opioids

Source: Centers for Disease Control and Prevention
Substance Exposure in Pregnancy

1. History
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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%)

Percentage of Women With an Opioid Pain Reliever in the 2nd or 3rd Trimester


@stephenwpatrick
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
State Medicaid variability in coverage of Opioid Agonist Therapies

Pregnant Women in Treatment Getting OAT

Analysis of the Substance Abuse and Mental Health Administration’s Treatment Episode Discharge Dataset. Sample: Pregnant women treated for opioid use disorder in FL, KY, MA, MI, MO, NY, NC, TN, WA, WV; 2013.
Percentage of OTPs and Buprenorphine Providers Accepting Insurance

*Medicaid: p<0.001; Private Insurance p=0.037; Cash Payments <0.001

Patrick SW, Buntin MB, Cooper WO. Barriers to Accessing Opioid Agonist Therapies. Under Review.
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

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGN</th>
<th>SCORE</th>
<th>Gastrointestinal disturbances</th>
<th>Respiratory/vasomotor disturbances</th>
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<tr>
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<td>High pitch/excessive cry Continuous (high pitched) cry</td>
<td>2, 3</td>
<td>Excessive sucking</td>
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<td>Sleeps less than 1 hour after feeds</td>
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<td>Poor feeding*</td>
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<td>Regurgitation*</td>
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<td>Sleeps less than 3 hours after feeds</td>
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<td>Projectile vomiting</td>
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<td>Hyperactive Moro reflex Markedly hyperactive Moro reflex</td>
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<td>Loose stools</td>
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<td>Mild tremors disturbed*</td>
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<td>Watery stools</td>
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<td>Mod/severe tremors disturbed*</td>
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<td>Frequent yawning (&gt; 3 – 4 in ½ hr)</td>
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<td>Generalised convulsions</td>
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<td>Nasal flaring</td>
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<td>Respiratory rate &gt; 60/min</td>
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<td>Respiratory rate &gt; 60/min and rejections</td>
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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 . . .

Credit: Madge Buus-Frank

@stephenwpattern
Opioid Prescribing and NAS

Predicting NAS

• Prescription opioids include
  – Short-acting (e.g. hydrocodone)
  – Long-acting (e.g. oxymorphone ER)
  – Maintenance (e.g. methadone, buprenorphine)

• Factors associated with developing NAS unclear
  – Dose (only evaluated for maintenance drugs)
  – Tobacco
  – Selective Serotonin Reuptake Inhibitor

• Data from Tennessee Medicaid, 2009-2011
## Characteristics of Mothers

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<thead>
<tr>
<th>Maternal race</th>
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N = 80,675 N = 31,354

p-value
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@stephenwpatrick

*Results shown after adjustment for maternal age, education, race, infant gender, birthweight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure (p<0.001), drug type and number of cigarettes smoked per day.

0%
5%
10%
15%
20%
25%
30%
35%
40%
45%
50%

Oxycodone HCl 10mg q6h x 5 weeks
Buprenorphine HCl 24mg q24h x 25 weeks

No SSRI, No Smoking
SSRI, No Smoking
No SSRI, Smoking 1 pack
SSRI and Smoking 1 pack

*Results shown after adjustment for maternal age, education, race, infant gender, birthweight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure (p<0.001), drug type and number of cigarettes smoked per day.
Next Steps

• Medicaid insures ~80% of infants with NAS
  – States well-positioned to minimize unnecessary opioid use in pregnancy
• The AAP recommends observation of opioid exposed infants for 4-7 days
  – Low-risk discharged sooner?
  – High-risk closer observation?
• Role of smoking cessation
More Opioids = More NAS?
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

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<th>2009</th>
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<th>2011</th>
<th>2012</th>
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<td><em><em>Mean Charges</em> (2012 US$)</em>*</td>
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*p<0.001


@stephenwpatrick
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<td>Mean Charges* (2012 US$)</td>
<td>$75,700</td>
<td>$80,500</td>
<td>$87,700</td>
<td>$93,400</td>
</tr>
</tbody>
</table>

*p<0.001

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


@stephenwpattern
# Total Hospital Charges for NAS, 2009-2012

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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</thead>
<tbody>
<tr>
<td>Medicaid*</td>
<td>$560M</td>
<td>$870M</td>
<td>$900M</td>
<td>$1.2B</td>
</tr>
<tr>
<td>Private Payer*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self Pay*</td>
<td></td>
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</tr>
<tr>
<td>Other Payer*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Charges*</td>
<td></td>
<td></td>
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*p<0.001

**Total Hospital Charges for NAS, 2009-2012**

<table>
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</tr>
<tr>
<td>Private Payer*</td>
<td>$130M</td>
<td>$170M</td>
<td>$210M</td>
<td>$200M</td>
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<tr>
<td>Self Pay*</td>
<td>$20M</td>
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</tr>
<tr>
<td>Other Payer*</td>
<td>$14M</td>
<td>$30M</td>
<td>$30M</td>
<td>$30M</td>
</tr>
<tr>
<td>Total Charges*</td>
<td>$730M</td>
<td>$1.1B</td>
<td>$1.2B</td>
<td>$1.5B</td>
</tr>
</tbody>
</table>

*p<0.001

Targets, Emerging Strategies and Issues
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)

SAMHSA Guidelines this Fall

• Dual purpose:
  – To increase the number of providers who can offer care to women with OUD who are pregnant and to their infants
  – To standardize this care throughout the United States

• Exhaustive literature review, RAND RAM

Emerging issues
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
Breastfeeding

- Breastfeeding safe and effective
  - Promotes bonding
  - Very little OAT medications in breastmilk
    - Recent blackbox warning for codeine, tramadol
  - Reduces LOS for NAS
  - Clear exclusion – HIV, HCV with cracked/bleeding nipples

- Academy of Breastfeeding Medicine
  - Appropriate: >90 days in treatment
  - Inappropriate: Active illicit use
  - Maybe: >30 days in treatment
Hepatitis C Prevalence Among Pregnant Women

Hepatitis C Prevalence Among Pregnant Women, Tennessee 2014


@stephenwpatrick
Hepatitis C Prevalence Among Pregnant Women, US 2014


@stephenwpatrick
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)


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Novel Improvement Efforts
Dartmouth

% Opioid-exposed Newborns Receiving Morphine

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>54</td>
<td>46%</td>
</tr>
<tr>
<td>Intervention Year 1</td>
<td>61</td>
<td>51%</td>
</tr>
<tr>
<td>Intervention Year 2</td>
<td>48</td>
<td>27%</td>
</tr>
</tbody>
</table>

% Opioid-exposed Newborns Receiving Adjunctive Agents

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>54</td>
<td>13%</td>
</tr>
<tr>
<td>Intervention Year 1</td>
<td>61</td>
<td>7%</td>
</tr>
<tr>
<td>Intervention Year 2</td>
<td>48</td>
<td>2%</td>
</tr>
</tbody>
</table>

N = opioid-exposed infants per year

Source: Bonny Whalen, MD and Alison Holmes, MD
@stephenwpatrick
Yale’s Approach To Scoring

• **Eat**
  > 1 oz or breastfeeding well

• **Sleep**
  > 1 hour undisturbed

• **Console**
  Within 10 minutes

Source: Matthew Grossman, MD, Yale
Yale: Proportion of Infants that Received Morphine

<table>
<thead>
<tr>
<th></th>
<th>Received Morphine (ESC)</th>
<th>Would Have Received Morphine (FNASS)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS infants (n=50)</td>
<td>6 (12%)</td>
<td>31 (62%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Source: Matthew Grossman, MD, Yale
Our Experience at Vanderbilt
• Admin: NICU always full, what can we do?
  – NAS ~10% of 96 bed NICU
• Neo/Peds: Let’s move babies out of the NICU, allow rooming in
• Pilot –
  – RN training, educational materials, RN/hospitalist/neonatologist buy-in
  – Babies with NAS from newborn to floor (allow rooming in)
Vanderbilt: Project HOPE

• Focus on family-centered care
• Interdisciplinary team
  – Newborn, NICU, General pediatrics, OB
  – RN, MD, SW, Child Life, Lactation

• Foundation
  – Data measurement, QI methods
  – Set collective goals
Vanderbilt: Project HOPE

- September 2017
  - Funded by The Memorial Foundation
- Data
  - Consistent practice?
  - Measure changes
- Child life -> volunteer cuddlers
- Lactation -> improve breastfeeding
- Work through PDSA cycles
NAS Summary - Priorities

- Focus on non-pharm care and rooming-in
- Be consistent (i.e. adhere to a protocol)
- Focus on scoring
- Look beyond the baby
  - Talk to OB
  - Work on transition home
History
Trends in Opioid Use
Substance Exposure in Pregnancy
NAS
Federal and State Policy
Care Across the Continuum

Birth

Pre-Pregnancy  Prenatal  Neonatal  Childhood & Beyond
EPIDEMIC: RESPONDING TO AMERICA’S PRESCRIPTION DRUG ABUSE CRISIS

2011

@stephenwpatrick
White House Plan

• Education
  – Parents, youth, and patients
  – Requiring prescribers to receive education on the appropriate and safe use, and proper storage and disposal of prescription drugs

• Monitoring
  – Every state with a Prescription Drug Monitoring Program
  – Work towards interstate interoperability
White House Plan

• **Proper Medication Disposal**
  – Develop convenient and environmentally responsible prescription drug disposal programs to help decrease the supply of unused prescription drugs in the home.

• **Enforcement**
  – Provide law enforcement with the tools necessary to eliminate improper prescribing practices and stop pill mills.
NAS Policy
PRENATAL DRUG USE AND NEWBORN HEALTH

Federal Efforts Need Better Planning and Coordination
GAO: Highlights

• NIH Funding from 2008-2013
  – $21.6 million

• 14 federal programs provide direct services

• Need coordination, suggest one HHS contact
  – “there is a risk that federal efforts may be duplicated, overlapping, or fragmented”
Rep Clark, Sen McConnell, Sen Casey, Rep Stivers introduce bill to help newborns suffering from opiate dependency
Protecting Our Infants Act, 2015

• Requests that HHS:
  • Review and improve coordination in HHS
  • Develop a strategy to address gaps in research and federal programs
  • Study and develop recommendations for preventing and treating prenatal opioid use and NAS
  • Improve data and public health response by supporting states and tribes

• Signed by President Obama in November 2015
Comprehensive Addiction and Recovery Act of 2016

• **Highlights:**
  - Broad approach to prevention, expansion of treatment inclusive of pregnant women and children
  - Improving Treatment for Pregnant and Postpartum Women
  - GAO report on NAS
  - Infant Plan of Safe Care
• **Signed by President Obama in July 2016; however, to date, not fully funded ($1B in treatment funds in 21st Century Cures Act)**

GAO: Government Accountability Office
Public Law No: 114-198
Drug Policy in the New Administration

• White House Office of National Drug Control Policy “Drug Czar”
  – Almost eliminated twice
  – Recent nominee for position, withdrew, nominated again

• Opioid Commission, led by Gov. Chris Christie

• Recent commitment to ~$500 million in funds to states to expand treatment by Sec. Tom Price

• Will approach focused on prevention, treatment expansion continue?

• There has been wide bipartisan support on the issue
State Policy
Tennessee: Criminal Justice vs. Public Health

- **Safe Harbor Act of 2013**
  - “ensure that family-oriented drug abuse or drug dependence treatment is available”
  - Treatment by 20\textsuperscript{th} week -> No prosecution, no child removal just for history of drug misuse

- **Public Chapter 820**
  - A woman can be charged with a misdemeanor if she illegally uses narcotics during pregnancy and if the baby is harmed as a result (ex. Neonatal Abstinence Syndrome)
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
Conclusions

• Opioid misuse is not new
• Recent rise of opioid use and NAS left the health system unprepared
• Public health approaches are needed
• Care for NAS needs standardization, be comprehensive and inclusive of mother’s needs
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American Academy of Pediatrics
Committee on Substance Use
of Prevention

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vu.edu/nas