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 For Opioid Therapies

## Understanding Neonatal Abstinence Syndrome for the General Pediatrician

Stephen Patrick, MD, MPH, MS, FAAP  
 August 23, 2017

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## 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.pcso-o.org

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## CME

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

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

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## Speaker



Stephen Patrick, MD, MPH, MS, FAAP

The speaker has no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.  
 Dr Patrick does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

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## 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.

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## >1827 Morphine marketed by Merck

- > Pain relief
- > Treatment of 'opium addiction'
- > Treatment of 'alcoholism'



Frakt, Austin. "Painkiller Abuse, a Cyclical Challenge." The New York Times 22 Dec. 2014.

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➤ **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.**

Frakt, Austin. "Painkiller Abuse, a Cyclical Challenge." The New York Times 22 Dec. 2014. Additional Source: Hendree Jones, PhD

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## NEJM 1980

Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.  
 2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. J Clin Pharmacol. 1978; 18:180-8.

**PROGNOSTIC VALUE OF IMMUNOLOGIC MARKERS IN ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA**

*To the Editor:* The letter from Dr. Bitran<sup>1</sup> 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.<sup>2</sup> There were 31 patients with multi-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

Porter J, Jick H. Addiction rate in patients treated with narcotics. N Engl J Med. Jan 10 1980;302(2):123.

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## NEJM 1980

Comprehensive drug surveillance. JAMA. 1970; 213:1455-60.  
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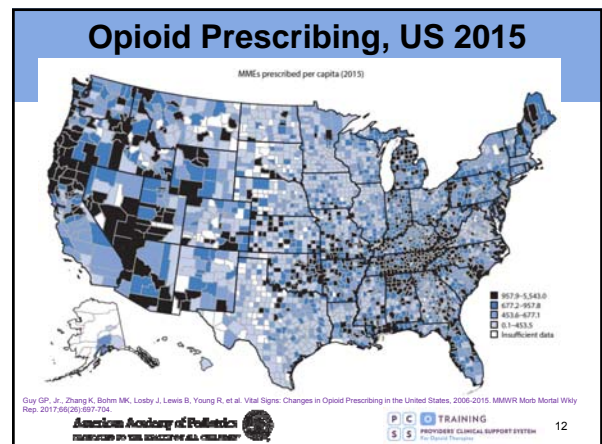
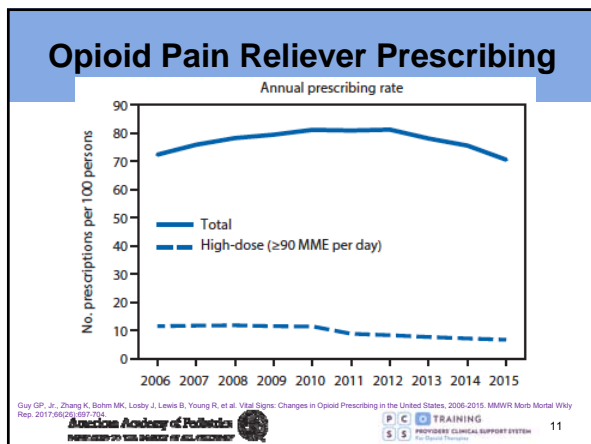
- 1996 • American Pain Society "Pain as the 5<sup>th</sup> Vital Sign Campaign"
- 1998 • Federation of State Medical Boards published "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."
- 2003 • The New York Times reports tripling of young adults (18-25) abusing opioid 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

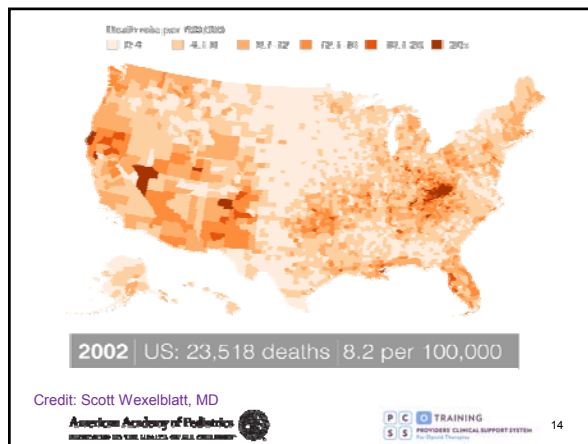
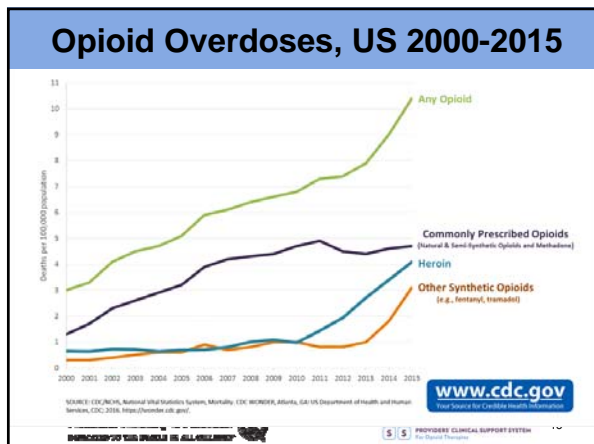
Frakt, Austin. "Painkiller Abuse, a Cyclical Challenge." The New York Times 22 Dec. 2014.

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### 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

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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

Substance Abuse and Mental Health Services Administration. Results from the 2015 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2016.

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

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### 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%)

Kozhimannil KB, Graves AJ, Levy R, Patrick SW. Predictors of Prescription Opioid Abuse Among Pregnant US Women. Women's Health Issues. 2017 Mar 31; pii: S1049-3867(16)30398-2. doi: 10.1016/j.whi.2017.03.001. [Epub ahead of print]

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### 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

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## 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




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## 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

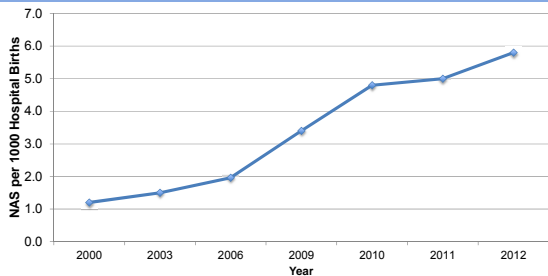



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## NAS Scoring Issues




- 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: Midge Buus-Frank  



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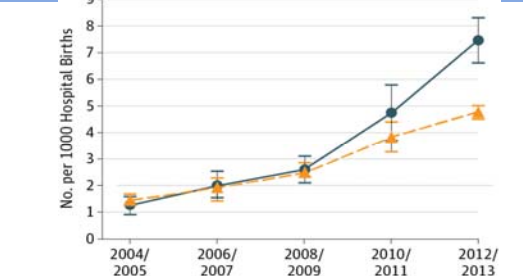
## Incidence of NAS in the US, 2000-2012






Patrick SW, et al. Neonatal Abstinence Syndrome and Associated Healthcare Expenditures – United States, 2000-2009. JAMA. 2012 May 9;307(18):1934-40.  
 Patrick SW, Davis MM, Lehman CU, Cooper WD. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol. Apr 30 2015.

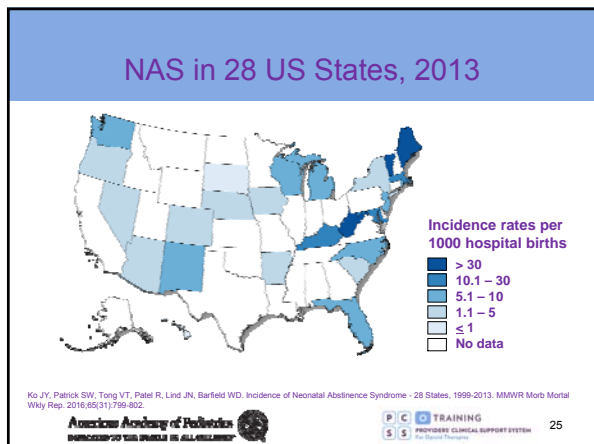



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## Neonatal Abstinence Syndrome in Rural vs. Urban Communities



Vilgiano NL, Wineman TN, Kothmann K, Davis MM, Patrick SW. Rural - Urban Differences Neonatal Abstinence Syndrome and Maternal Opioid Use, 2004-2015. JAMA Pediatrics. 2016 Dec 12.




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### Mean LOS and Hospital Charges for NAS, 2009-2012

	2009	2010	2011	2012
Mean LOS (day)	22.7	22.9	22.8	23.0
Mean Charges* (2012 US\$)				

\*p<0.001

Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol.* 2015;35(8):650-655.

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### Mean LOS and Hospital Charges for NAS, 2009-2012

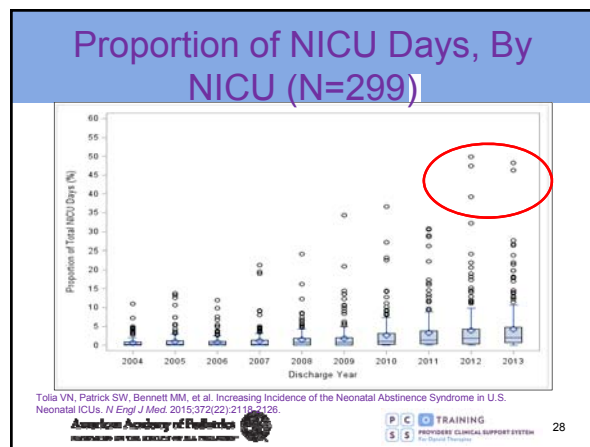
	2009	2010	2011	2012
Mean LOS (day)	22.7	22.9	22.8	23.0
Mean Charges* (2012 US\$)	\$75,700	\$80,500	\$87,700	\$93,400

\*p<0.001

Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol.* 2015;35(8):650-655.

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

	2009	2010	2011	2012
Medicaid*	\$560M	\$870M	\$900M	\$1.2B
Private Payer*				
Self Pay*				
Other Payer*				
Total Charges*				

\*p<0.001

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

	2009	2010	2011	2012
Medicaid*	\$560M	\$870M	\$900M	\$1.2B
Private Payer*	\$130M	\$170M	\$210M	\$200M
Self Pay*	\$20M	\$40M	\$30M	\$40M
Other Payer*	\$14M	\$30M	\$30M	\$30M
Total Charges*	\$730M	\$1.1B	\$1.2B	\$1.5B

\*p<0.001


Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol.* 2015;35(8):650-655.



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## 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






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## 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



Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US Children’s Hospitals. 2004-2011. *J Perinatol*. 2014.  
 Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5).


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## 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)

Hall ES, Weverblatt SL, Crowley M, et al. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e527-534.  
 Patrick SW, Schumacher RE, Horbar JD, et al. Improving Care for Neonatal Abstinence Syndrome. *Pediatrics*. 2016;137(5).

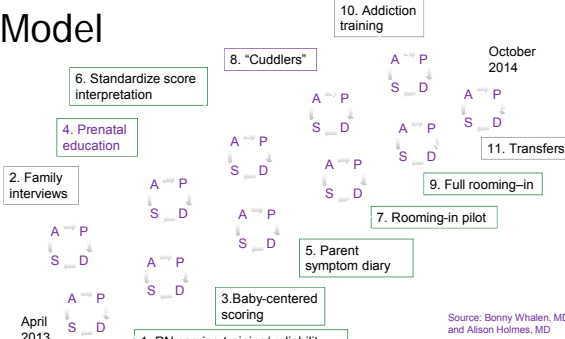

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## Rooming In



- 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


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## Dartmouth as a Model



Source: Bonny Whalen, MD and Alison Holmes, MD


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## Dartmouth

### % Opioid-exposed Newborns Receiving Morphine



Time Point	%	N
Baseline (3/1/12-2/28/13)	46%	54
Intervention Year 1 (3/1/13-2/28/14)	51%	61
Intervention Year 2 (3/1/14-2/28/15)	27%	48

### % Opioid-exposed Newborns Receiving Adjunctive Agents

Time Point	%	N
Baseline (3/1/12-2/28/13)	13%	54
Intervention Year 1 (3/1/13-2/28/14)	7%	61
Intervention Year 2 (3/1/14-2/28/15)	2%	48



N = opioid-exposed infants per year

Holmes AV, Atwood EC, Whalen B, et al. Rooming-In to Treat Neonatal Abstinence Syndrome: Improved Family-Centered Care at Lower Cost. *Pediatrics*. 2016;137(6).


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## Breastfeeding

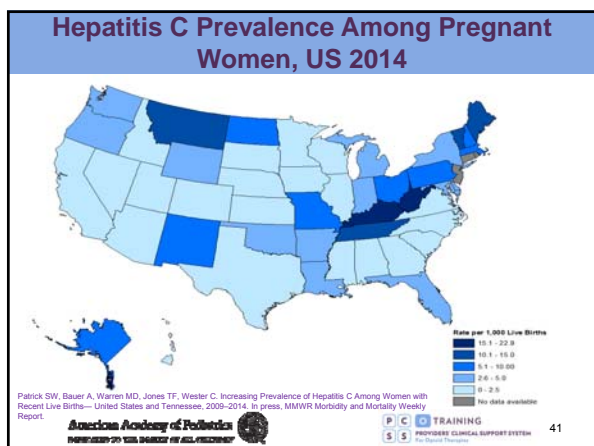
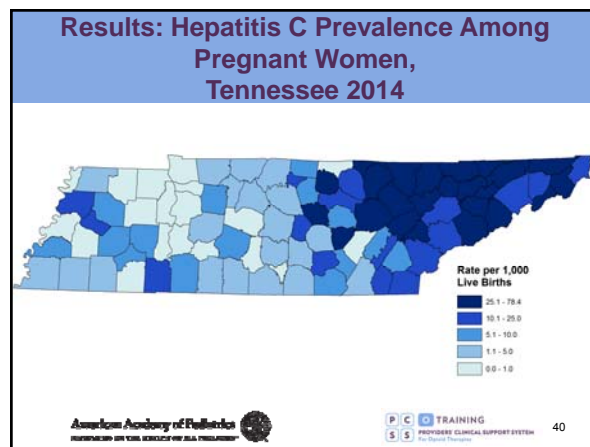
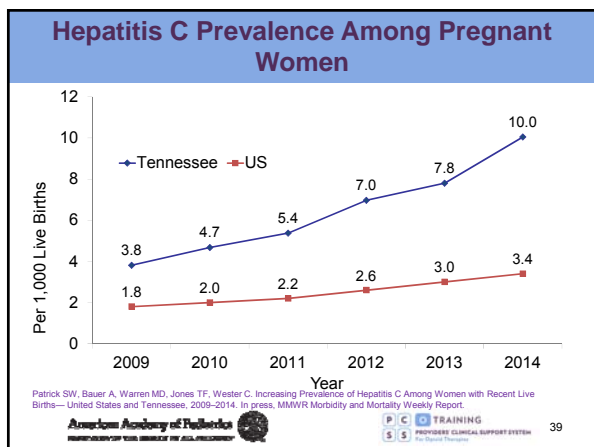
- Breastfeeding safe and effective
  - Promotes bonding
  - Very little MAT medications in breastmilk
  - Reduces LOS for NAS
- American Breastfeeding Medicine
  - Appropriate: >90 days in treatment
  - Inappropriate: Active illicit use
  - Maybe: >30 days in treatment



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## 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 of 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)

Patrick SW, Burke JF, Biel TJ, Auger KA, Goyal N, Cooper WO. Risk of Hospital Readmission Among Infants with Neonatal Abstinence Syndrome. *Hospital Pediatrics*. 2015 Oct;5(10):513-9. doi: 10.1542/hpeds.2015-0024  
Makouf FI, MD, Cooper WO, Slaughter C, Dudley J, Patrick SW. Outpatient Treatment of Neonatal Abstinence Syndrome Associated with Longer Treatment and Higher Rates of Healthcare Utilization.  


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## 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



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## Long-Term Outcomes







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## 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







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## 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?







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## 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

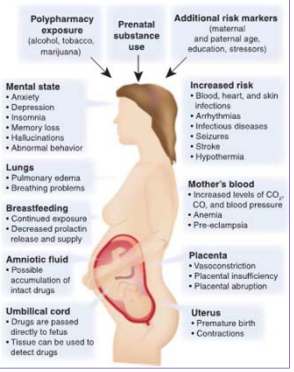





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## Drug effects do not appear in isolation



- Polysubstance use
- Maternal clinical comorbidities
- Maternal psychiatric conditions





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## 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)







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## Neurodevelopmental Outcomes









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## 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 TS, Johnson HL. Long-term effects of prenatal methadone maintenance. *NIDA research monograph*. 1985;59:73-83.







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## Behavior

- 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 TS, Johnson HL. Long-term effects of prenatal methadone maintenance. *NIDA research monograph*. 1985;59:73-83.







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## Behavior

- 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

Rosen TS, Johnson HL. Long-term effects of prenatal methadone maintenance. *NIDA research monograph*. 1985;59:73-83.







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## 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

Lifschitz MH, Wilson GS, Smith EQ, Desmond MK. Factors affecting head growth and intellectual function in children of mothers with substance use disorders. *Am J Psychiatry*. 2014;171:274-281.







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## Additional Studies

- NAS vs. controls, 6 months (McGlone 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







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## Summary of Outcomes

Short-term Effects/Birth Outcomes	
Fetal growth	Effect
Anomalies	No effect
Withdrawal	Strong effect
Neurobehavior	Effect
Long-term Outcome	
Growth	No effect
Behavior	Effect
Cognition	No consensus on effect
Language	Limited or no data
Achievement	Limited or no data


Behnke M, Smith VC. Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics*. 2013;131(3):e1009-1024.


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How about the environment?


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## 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


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## 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

Did you live with anyone who was depressed, mentally ill, or suicidal?

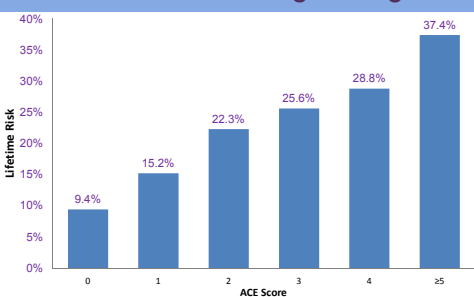
Did you ever see your mother hit, slapped, kicked, punched, or beat up?

Did a parent or adult in the home ever swear at you, insult you, or put you down?

Credit: Ruth Ann Shepherd, MD



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## ACES and Risk of Illegal Drug Use




ACE Score	Lifetime Risk
0	9.4%
1	15.2%
2	22.3%
3	25.6%
4	28.8%
≥5	37.4%

Dube, S. R., et al. (2003). "Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study." *Pediatrics* 111(3): 564-572.


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## Summary


- 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


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## 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





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## 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







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## More to come ...


- Update to 2012 AAP policy statement on drug withdrawal.





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## 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.  
 ♦ The AAP designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.  
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 ♦ This program is accredited for 1.0 NAPNAP CE contact hours of which 0 contain pharmacology (Rx), (0 related to psychopharmacology) (0 related to controlled substances), content per the National Association of Pediatric Nurse Practitioners (NAPNAP) Continuing Education Guidelines.





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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](http://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](mailto:pcss-o@aaap.org).



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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 (IntNSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: [www.pcss-o.org](http://www.pcss-o.org)

For questions email: [pcss-o@aaap.org](mailto:pcss-o@aaap.org)

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