

The Problem of Neonatal Abstinence Syndrome



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U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

What is Neonatal Abstinence Syndrome (NAS)?

- **Drug withdrawal syndrome that occurs primarily among opioid-exposed infants shortly after birth**
- **Withdrawal symptoms most commonly occur 48–72 hours after birth**
 - Tremors, hyperactive reflexes, seizures
 - Excessive or high-pitched crying, irritability, yawning, stuffy nose, sneezing, sleep disturbances
 - Poor feeding and sucking, vomiting, loose stools, dehydration, poor weight gain
 - Increased sweating, temperature instability, fever



Additional Effects of NAS

➤ In utero effects:

- Poor fetal growth
- Preterm birth

➤ Postnatal effects:

- Prolonged hospitalization (including NICU admission)
- Poor postnatal growth, dehydration, and seizures

➤ Data on long-term developmental outcomes related to NAS are limited



Exposures Associated with NAS

➤ **Most commonly attributed to exposure to opioids**

- Pain relievers: Vicodin[®], OxyContin[®], Percocet[®]
- Illicit substances: Heroin
- Opioid maintenance therapy: Methadone, buprenorphine
 - Maintenance therapy: Long-term treatment for opioid use disorder, under medical supervision, with a longer-acting but less euphoric opioid
 - Recommended by ACOG during pregnancy

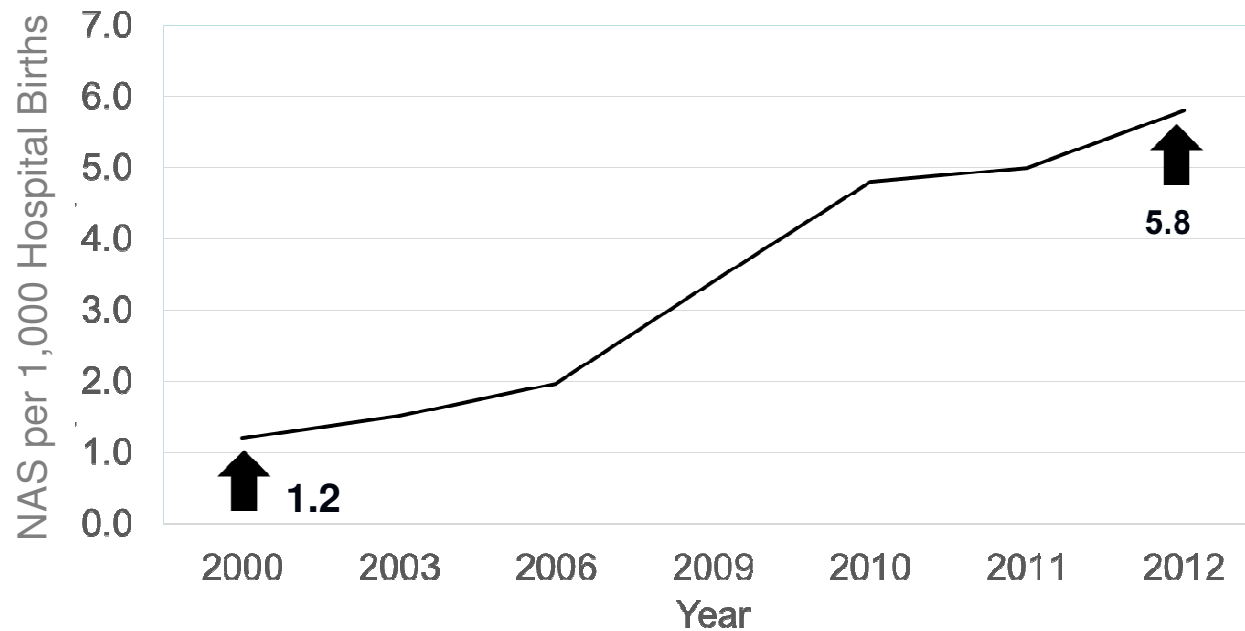
➤ **Cocaine, amphetamines, and barbiturates have also been implicated**



Terminology Related to Opioids

- **Opioid use: Taking an opioid to reduce pain**
 - Broad category includes morphine, codeine, synthetic opioids (e.g., fentanyl or methadone) and semisynthetic opioids (e.g., oxycodone)
- **Opioid abuse or misuse: Use of prescription drugs without a prescription, or in a manner other than as directed by the prescriber**
- **Opioid dependence: Physiologic adaptation to opioids that produces symptoms of withdrawal when opioids are stopped**
- **Opioid use disorder: Problematic pattern of opioid use leading to clinically significant impairment or distress**

Incidence of NAS in the United States, 2000–2012



Patrick SW, Schumacher RE, Benneyworth BD, et al. *JAMA*. 2012;307(18):1934-40.

Patrick SW, Davis MM, Lehmann CU, et al. *J Perinatol*. 2015 Aug;35(8):650-5.

Increase in Affected Infants

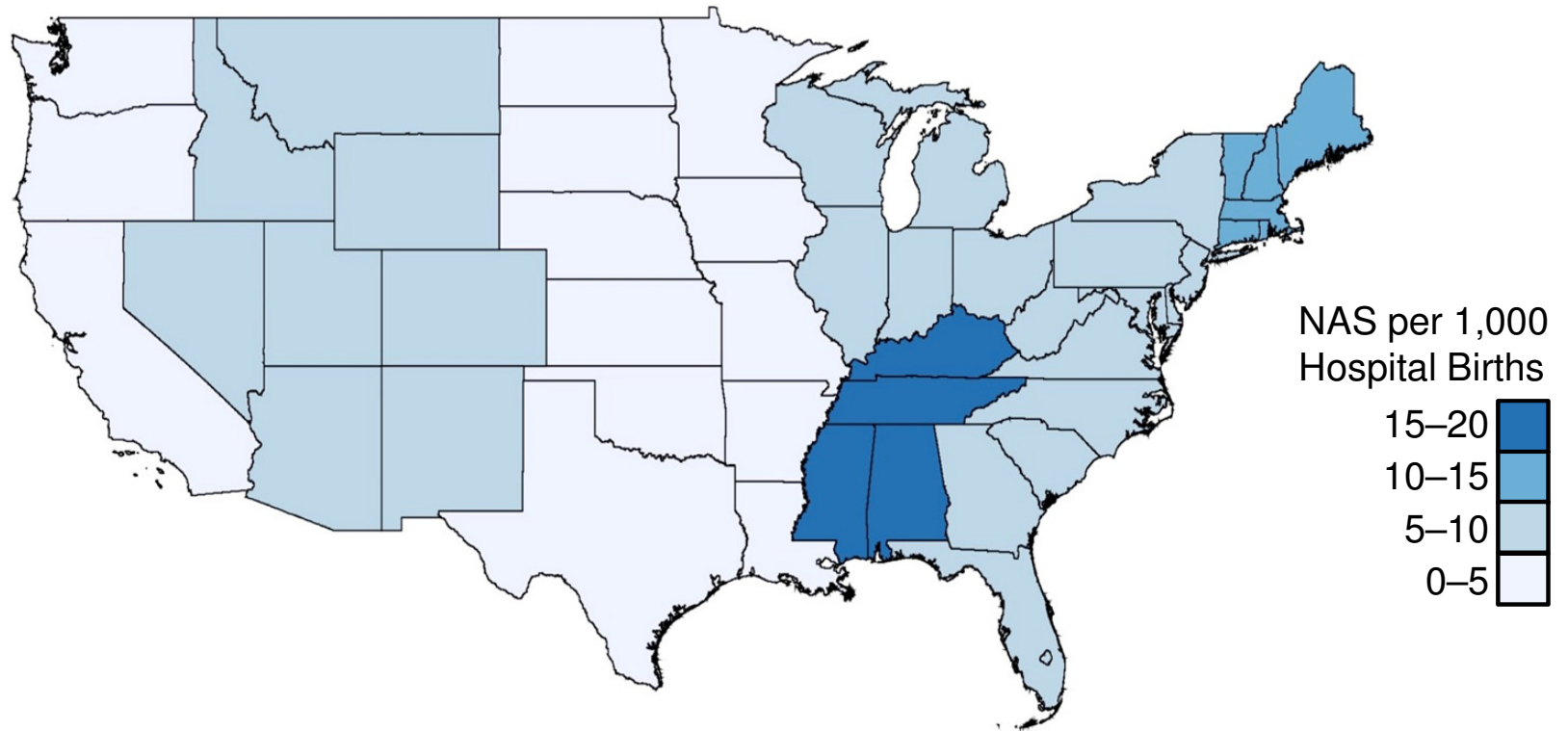
- **2,920 in the year 2000**
- **21,732 in the year 2012**
- **In 2012, one infant with NAS was born every 25 minutes**



Patrick SW, Schumacher RE, Benneyworth BD, et al. *JAMA*. 2012;307(18):1934-40.

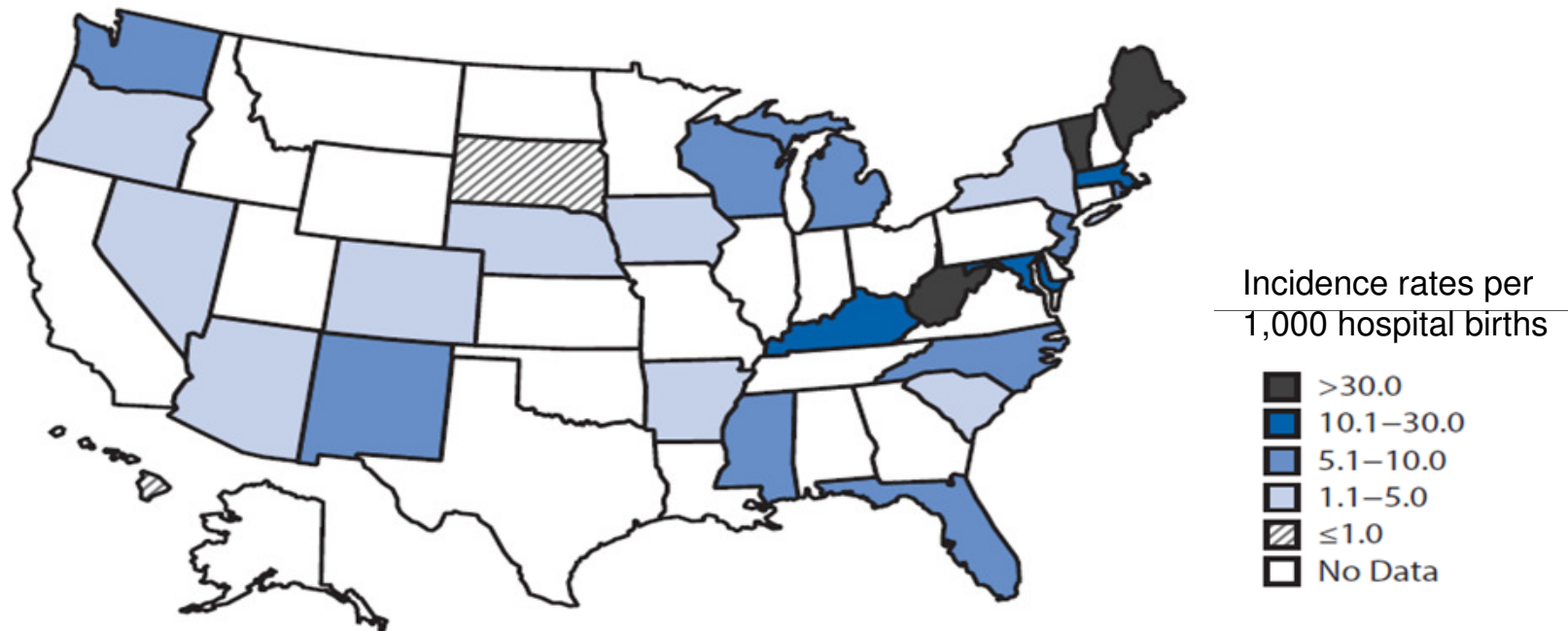
Patrick SW, Davis MM, Lehmann CU, et al. *J Perinatol*. 2015 Aug;35(8):650-5.

NAS Incidence by Geographic Region, 2012



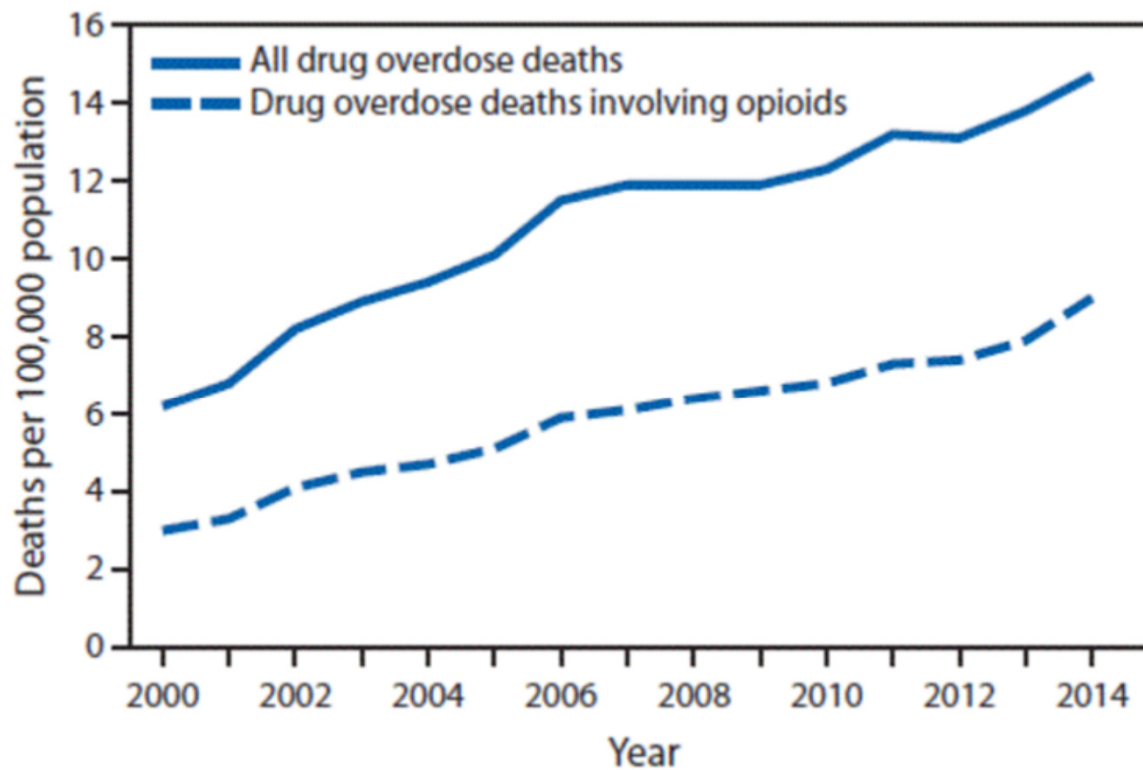
Patrick SW, Davis MM, Lehmann CU, et al. *J Perinatol.* 2015 Aug;35(8):650-5.

Incidence of Neonatal Abstinence Syndrome 25 States, 2012–2013



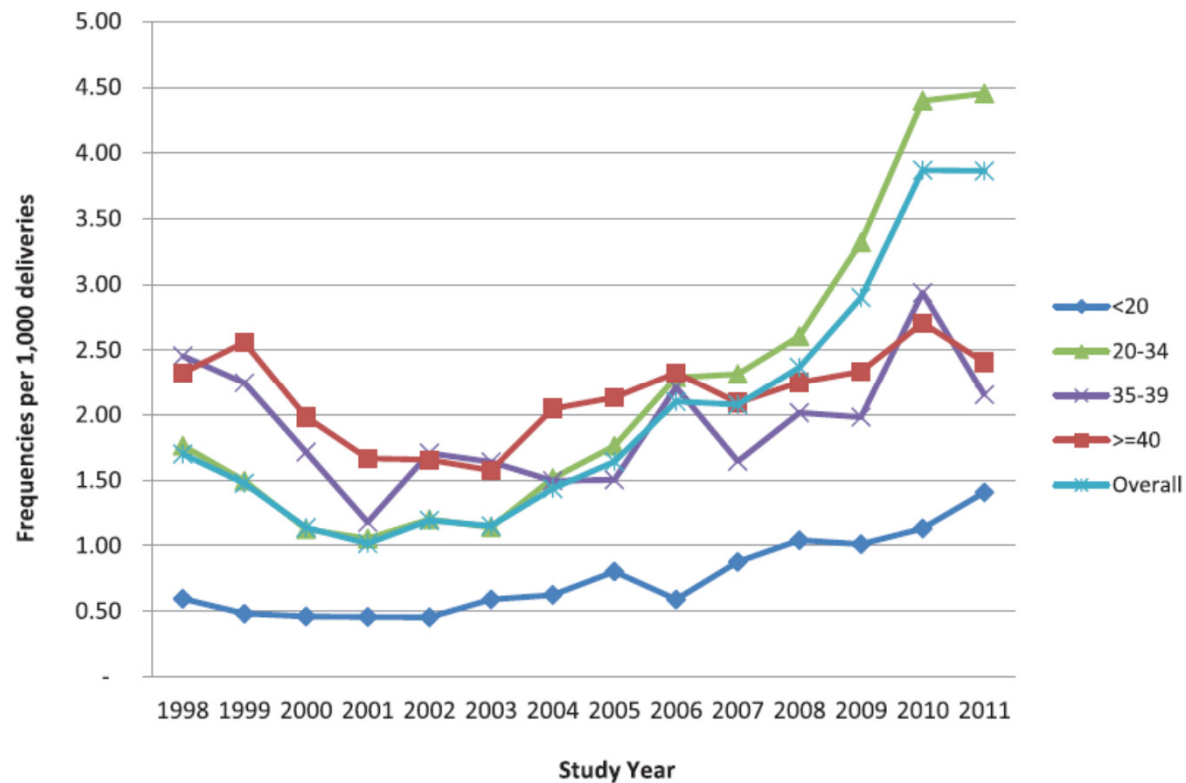
Ko JY, Patrick SW, Tong VT, et al. *MMWR Morb Mortal Wkly Rep.* 2016;65:799–802.

NAS and the Prescription Opioid Epidemic



Age-adjusted rate of drug overdose deaths and drug overdose deaths involving opioids in the United States, 2000–2014

Opioid Abuse and Dependence Among Pregnant Women



Opioid abuse or dependence per 1,000 deliveries, overall and by age in the U.S., 1998–2011

Prescribing of Opioids to Women of Reproductive Age

Opioid Prescription Claims by Type of Health Insurance Among Women of Reproductive Age (15–44 years), United States, 2008–2012



Ailes EC, Dawson AL, Lind JN, et al. *MMWR*. 2015 Jan 23;64(2):37-41.

Challenges in Preventing Opioid Use Prior to Conception



- **Nearly 50% of all pregnancies in the United States are unintended**
- **86% of pregnancies are unintended among women who abuse opioids**
- **Women using opioids may not initially know they are pregnant**

Finer LB, Zolna MR. *N Engl J Med.* 2016;374:843-852.

Heil SH, Jones HE, Arria A, et al. *J Subst Abuse Treat.* 2011 Mar;40(2):199-202.

Infants with NAS: Treatment and Costs

- **Exposed infants can require pharmacologic treatment (e.g. morphine, methadone, phenobarbital)**
 - 30%, 68%, and 91% of NAS infants required pharmacologic treatment in separate studies
- **Mean length of hospital stay: 23 days**
- **Mean hospital charge: \$93,400 per infant**
- **Total cost: \$1.5 billion**
 - Medicaid is most common payer (\$1.2 billion)



Strauss ME, Andresko M, Stryker JC, et al. *Am J Obstet Gynecol.* 1974 Dec 1;120(7):895-900.
Ebner N, Rohrmeister K, Winklbaur B, et al. *Drug Alcohol Depend.* 2007 Mar 16;87(2-3):131-8.
Patrick SW, Davis MM, Lehmann CU, et al. *J Perinatol.* 2015 Aug;35(8):650-5.
Kuschel C. *Semin Fetal Neonatal Med.* 2007 Apr;12(2):127-33.
Greig E, Ash A, Douiri A. *Arch Gynecol Obstet.* 2012 Oct;286(4):843-51.

It's Not Just About the Baby



➤ **Public health approach is needed to provide prevention of opioid use disorder across the lifespan for:**

- Neonates and infants
- Pregnant mothers
- Women and men of reproductive age prior to conception
- Youth
- Older adults

Beyond the Tip of the Iceberg: NAS Prevention and Preconception Health



Cheryl S. Broussard, PhD

Health Scientist, Birth Defects Branch

National Center on Birth Defects and Developmental Disabilities

Opioid Prescription Use Among Women of Reproductive Age and Pregnant Women



According to U.S. estimates:

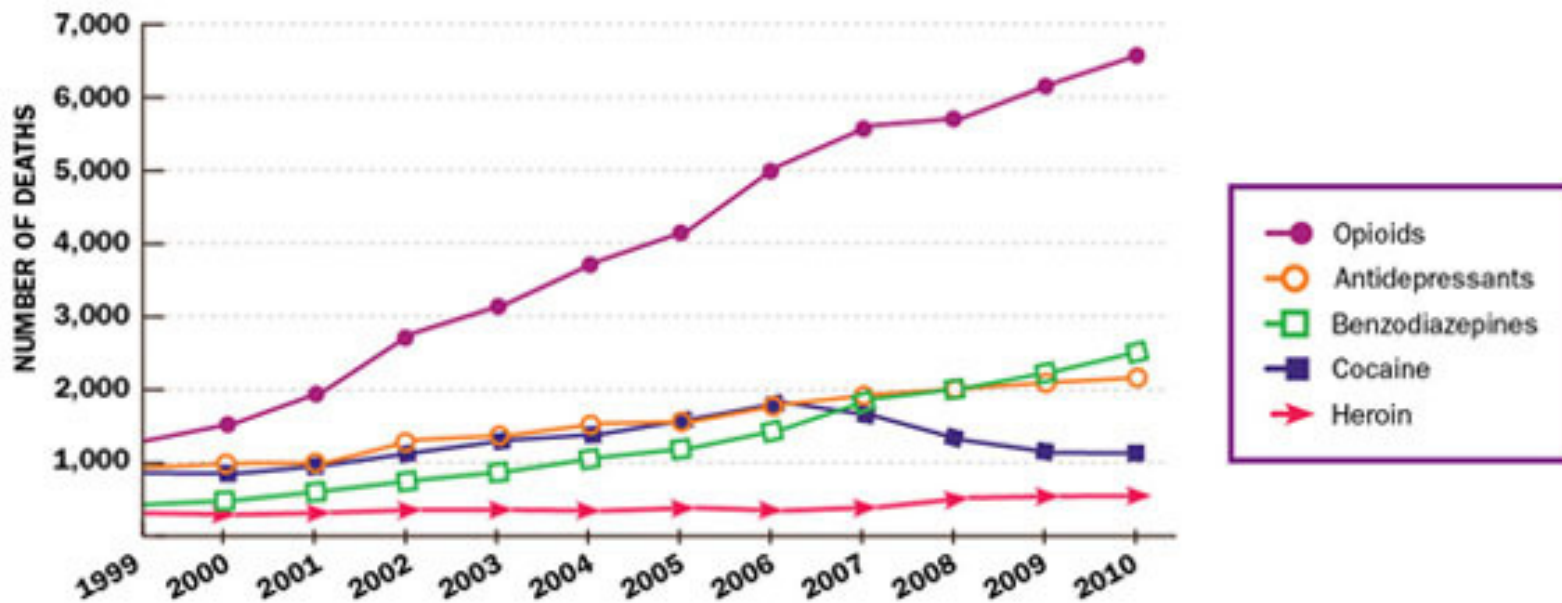
- One third of reproductive-aged women filled a prescription for an opioid medication
- 14%–22% of women filled an opioid medication prescription during pregnancy

Ailes EC, Dawson AL, Lind JN, et al. *MMWR*. 2015 Jan 23;64(2):37-41.

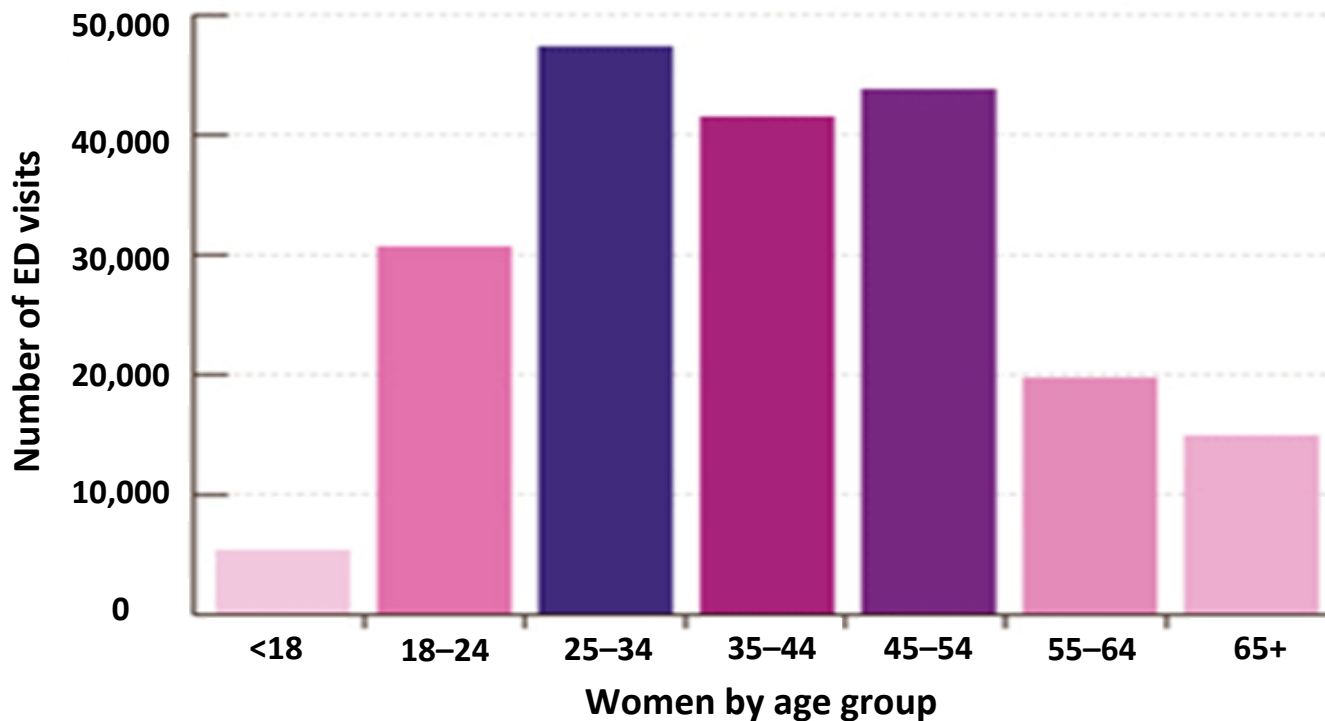
Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. *Anesthesiology*. 2014 May;120(5):1216-24.

Desai RJ, Hernandez-Diaz S, Bateman BT, et al. *Obstet Gynecol*. 2014 May;123(5):997-1002.

Drug Overdose Deaths Among Women



Every 3 Minutes, a Woman Goes to the Emergency Department for Prescription Pain Reliever Misuse or Abuse



Women between the ages of 25 and 54 are most likely to go to the emergency department because of prescription opioid misuse or abuse

Three Pillars of CDC's Work to Reverse the Prescription Drug Overdose Epidemic

- **Improve data** quality and track trends
- **Strengthen state efforts** by scaling up effective public health interventions
- **Supply health care providers with resources** to improve patient safety



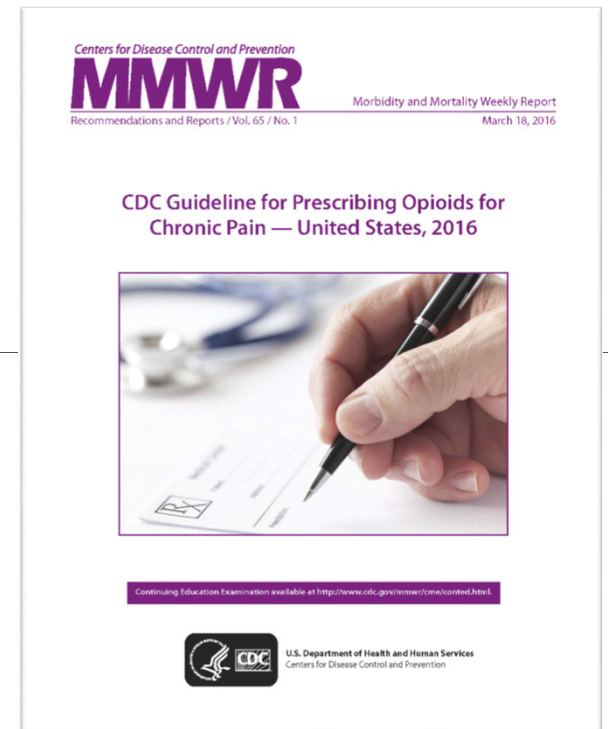
Primary Prevention Opportunities for NAS



Guideline for Prescribing Opioids for Chronic Pain

Outside of Active Cancer, Palliative, and End-of-life Care

Primary Care



Dowell D, Haegerich TM, Chou R. *MMWR Recomm Rep* 2016;65(No. RR-1):1–49.

Excerpts from CDC Recommendations: Providers for Preconception and Pregnant Women

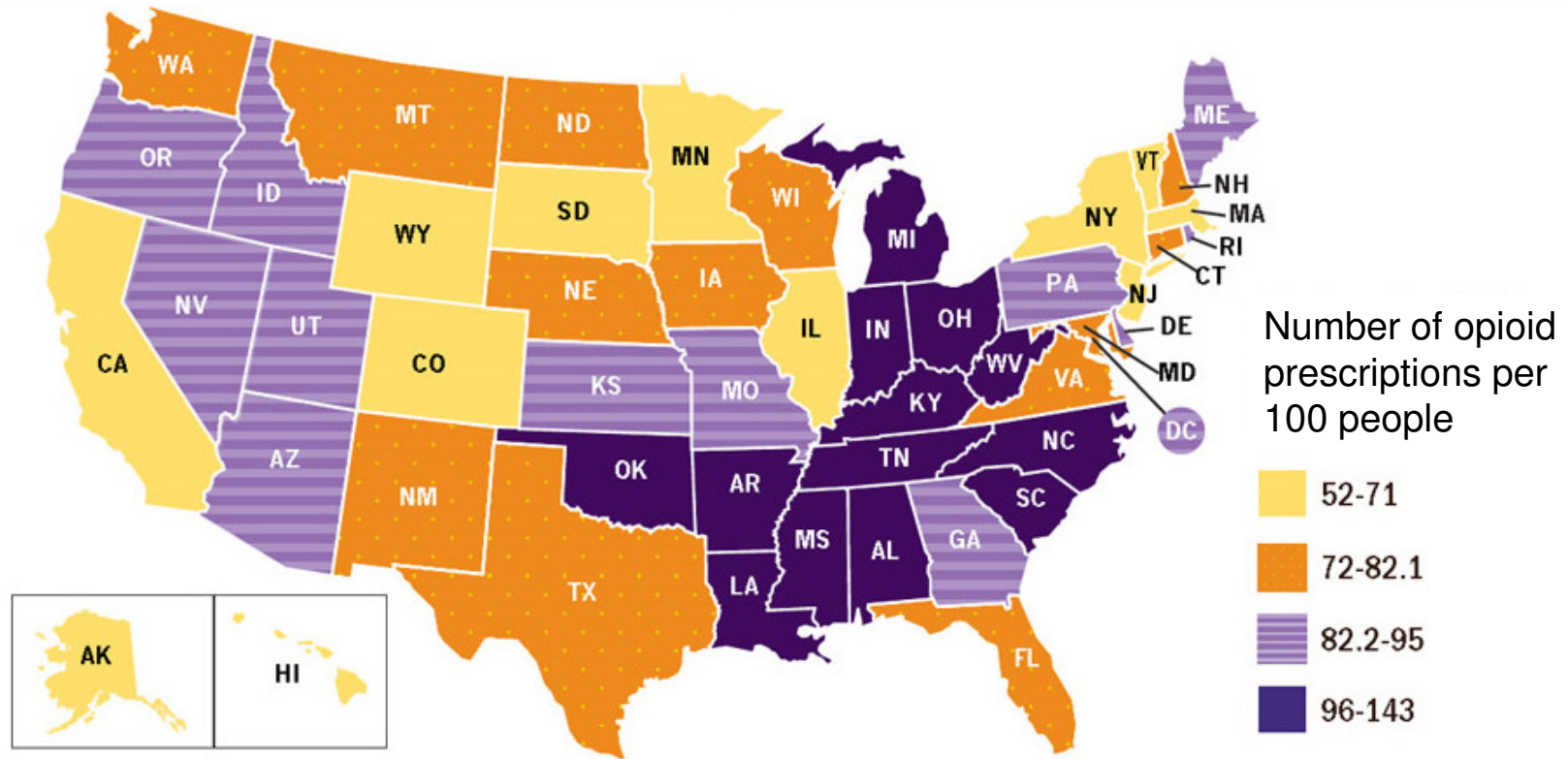
- **Before initiating opioid therapy for chronic pain for reproductive-aged women, discuss family planning and how long-term opioid use might affect any future pregnancy**
- **Carefully weigh risks and benefits with pregnant patients when making decisions about whether to initiate opioid therapy**



Excerpts from CDC Recommendations: Providers for Pregnant Women

- **For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered**
 - Access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the patient and fetus (e.g., spontaneous abortion and premature labor) if the patient goes into withdrawal
- **Arrange for delivery at a facility prepared to evaluate and treat neonatal abstinence syndrome**

Some States Have Higher Opioid Prescribing Rates, 2012

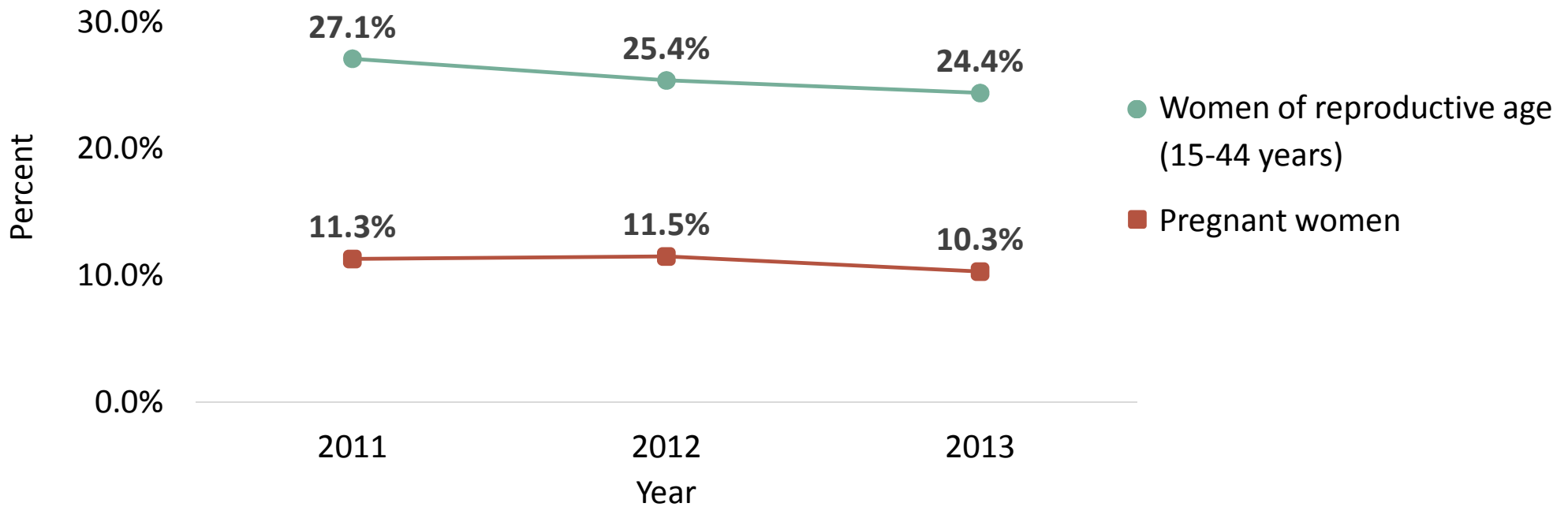


Prescription Drug Monitoring Programs (PDMPs)

- **State-based databases of controlled prescription drugs dispensed by pharmacies**
- **Currently in 49 states (not Missouri)**
- **Contain critical clinical data that can help**
 - Identify patients at risk for opioid-related overdoses
 - On high total doses, receiving from multiple sources
 - Inform providers of other medications the patient is receiving that may interact with those prescribed
 - Identify patients struggling with opioid use disorder

Evidence of Decreasing Opioid Use Before and During Pregnancy

Women who used a prescription opioid medication, U.S. commercial claims, 2011–2013

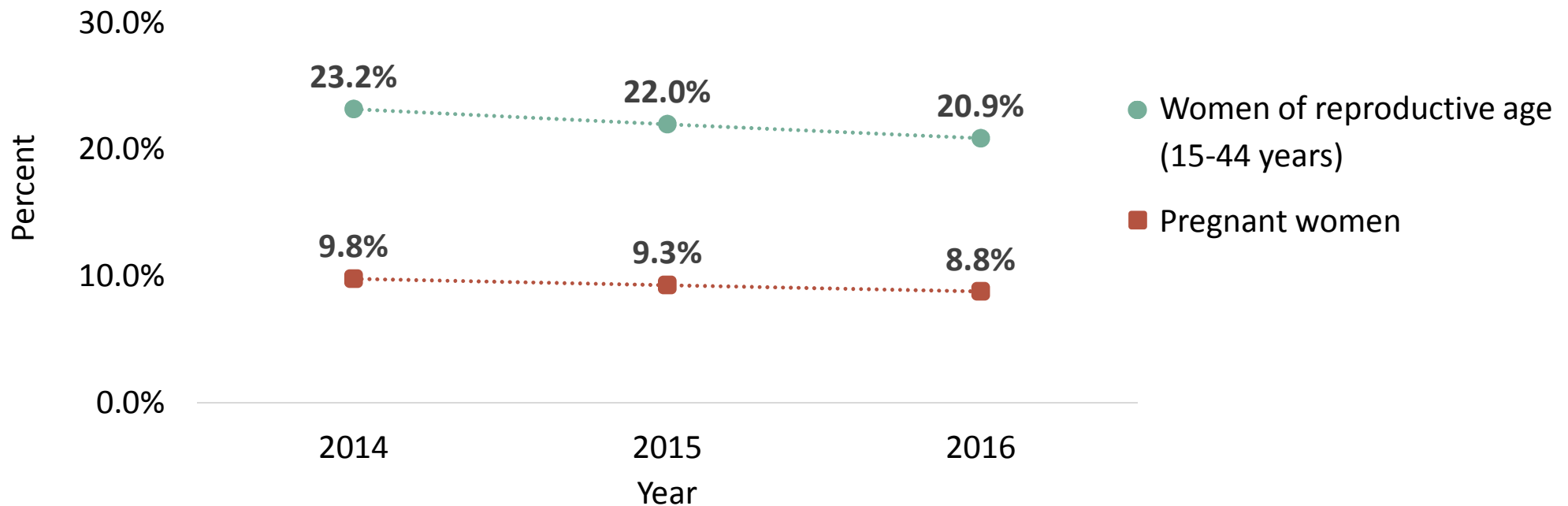


CDC, unpublished data

Truven Health Analytics MarketScan® Treatment Pathways V3.0 Commercial claims database

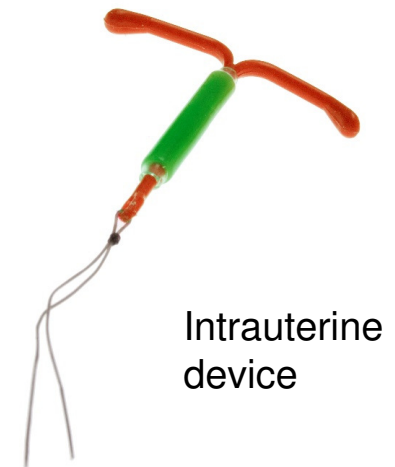
Projected Decrease in Opioid Use Before and During Pregnancy

Women who used a prescription opioid medication, U.S. commercial claims, 2014–2016



Primary Prevention Opportunities for NAS

- **Increased access to effective contraception both pre-pregnancy and post-delivery, including support for long-acting reversible contraception (LARC)**
 - Intrauterine devices (IUDs)
 - Contraceptive implants



Intrauterine device

CDC's Treating for Two Initiative



Expand and accelerate research to fill knowledge gaps



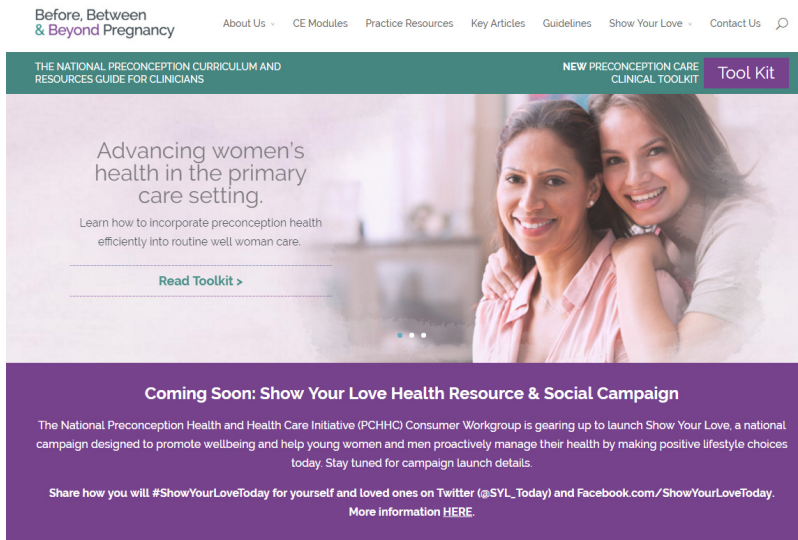
Evaluate evidence to facilitate reliable guidance



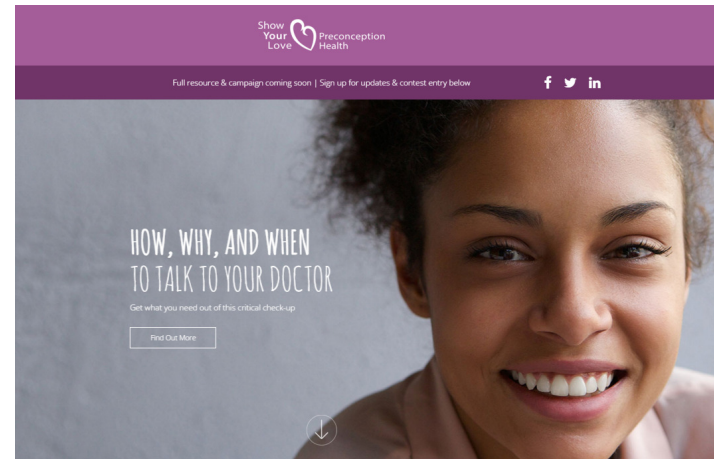
Deliver up-to-date information to support decision-making among prescribers, pharmacists, and consumers



Our vision: All women and men of reproductive age will achieve optimal health and wellness, fostering a healthy life course for them and any children they may have.



Before & Beyond
 Health Care Provider Resource & Training
 More About PCHHC & Partnership Information
www.beforeandbeyond.org | Twitter: @PCHHC

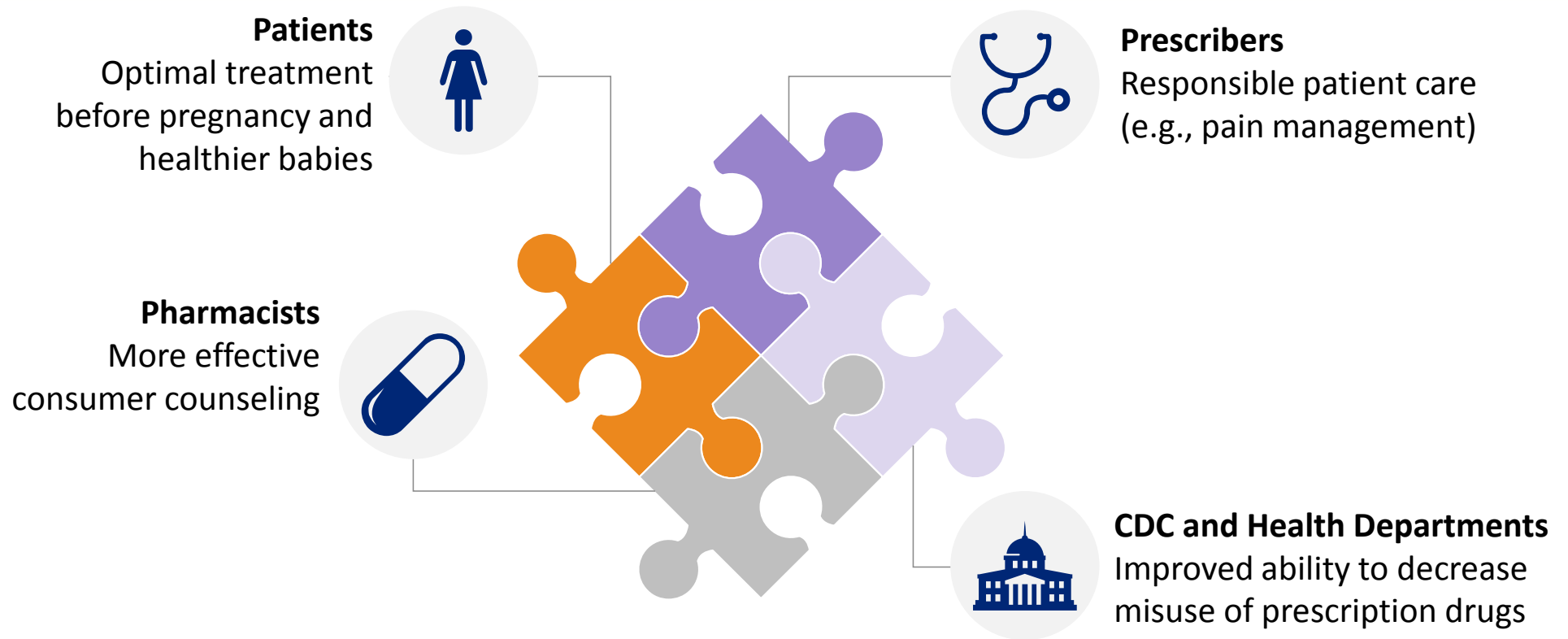


SHOW YOUR LOVE IS A NATIONAL CAMPAIGN DESIGNED TO PROMOTE WELLBEING AND SUPPORT YOUNG WOMEN AND MEN STRIVE TO ACHIEVE THEIR GOALS AND MAKE HEALTHY LIFESTYLE CHOICES TODAY.

Show Your Love
 First National Consumer Preconception Health Resource & Social Campaign
www.showyourlovetoday.com | Twitter: @SYL_Today

Five PCHHC Workgroups: Clinical | Consumer | Public Health | Surveillance and Data | Policy and Finance

Public Health Impact of Improved Preconception Health Care and Appropriate Opioid Prescribing



Summary

- **Trend data indicate decreases in opioid prescribing during pregnancy but at population level exposure is still high**
- **Aim is optimal treatment for women with opioid use disorder, including maintenance therapy when indicated**
- **Prevention strategies for NAS include not only decreasing exposure to opioids through evidence-based prescribing, but also broader attention to preconception health, including increased use of LARC**

Prescription Opioid and Substance Use in Pregnancy: Screening and Treatment



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Professor, Psychiatry, Epidemiology, Obstetrics, Gynecology, and Reproductive Sciences

Yale University School of Medicine

Considerations with Regard to Screening for Substance Use in Women During the Perinatal Period

Which women should be screened?

When should they be screened?

What substances should they be screened for?

Considerations with Regard to Screening for Substance Use in Women During the Perinatal Period

How should women be screened?

What screening instruments should be used?

What are the consequences of screening?

Who Should Be Screened?

➤ Should screening be limited to some “high risk groups”?

- Pregnant women with a history of substance use prior to pregnancy
- Pregnant adolescents
- Clinics with women of color or lower socioeconomic groups

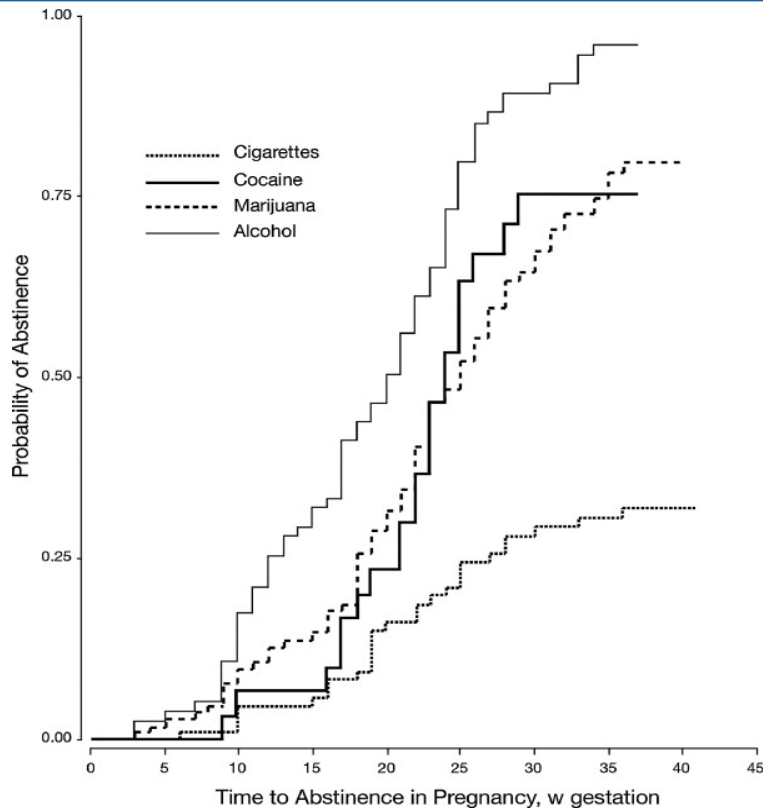
➤ The case of Pinellas County, Florida

- 15.4% of white women and 14.1% of black women were positive for a substance when urine was tested
- The rate of reporting was 10-fold higher for black than white women despite similar rates of positive screens
- Poverty was a predictor of reporting



When to Screen?

Time to Abstinence Differs Across Pregnancy



➤ Early screening will lead to higher rates of detection and can identify women who need assistance, but may also identify women who are likely to attain abstinence (quit a substance)

83% of all women were able to quit at least one substance. Pregnancy-related abstinence rates were high for all substances except cigarettes.

Screening for Substance Use in Pregnancy Using Biomarkers

- **Urine: easily accessible, limited windows of detection, poor performance for alcohol**
- **Blood: extremely limited window of detection**
- **Hair: broad window of detection but expensive and can be influenced by hair treatments**
- **Meconium: broad window of detection but expensive, limited to postpartum period**
- **Umbilical cord: broad window of detection but expensive, limited to postpartum period**
- **Saliva: accessible but reliability issues**

How Should Screening Be Conducted?

Screening Questionnaires vs Biological Assays

➤ Questionnaires

- Have flexible screening windows, e.g., prior week, month, year, duration of pregnancy
 - Can ask about substances that may not be included on a urine or other test
 - Can promote dialogue between patients and health care providers
 - Are inexpensive
- **Questionnaires can lead to false negative results, particularly for substances that are highly stigmatized (such as opiates)**

Which Screening Instruments Should Be Used?

- **Few screening instruments have been evaluated for use among pregnant woman, and most studies have not been replicated**
 - **CRAFFT (Car, Relax, Alone, Forget, Family/Friends, Trouble)**
 - Example question: Do you ever use alcohol or drugs while you are by yourself, alone?
 - **4Ps/4Ps plus/5 Ps (Parents, Partner, Past, Pregnancy)**
 - “Plus” question: Have you ever drunk beer, wine, or liquor?
 - **Wayne Indirect Drug Use Screener**
 - Example true or false statement: In the past year I have smoked at least 100 cigarettes.
 - **Substance Use Risk Profile-Pregnancy (SURP-P)**
 - Example question: In the month before you knew you were pregnant, how much beer, wine, or liquor did you drink?

ceasar-boston.org/CRAFFT/index.php

acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Opioid-Abuse-Dependence-and-Addiction-in-Pregnancy

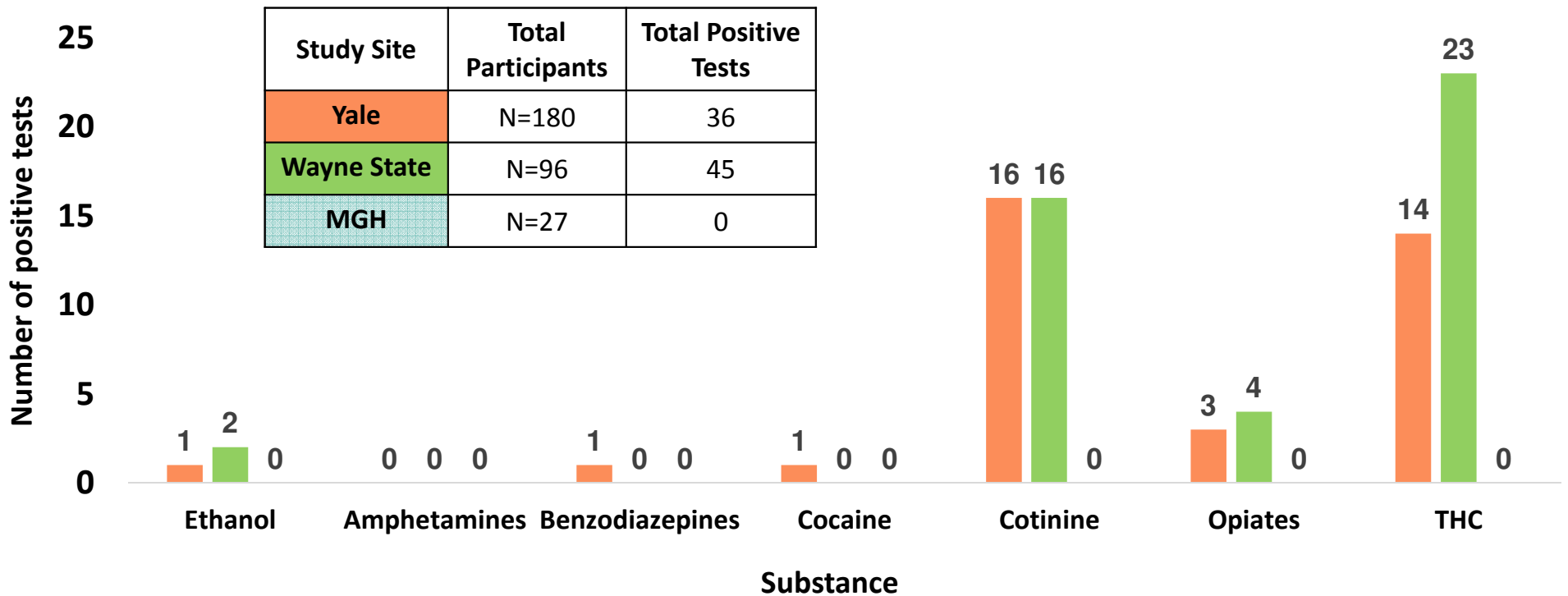
Undersma SJ, Svikis DS, LeBreton JM, et al. *Addiction*. 2012 Dec;107(12):2099-106.

Yonkers KA, Gotman N, Kershaw T, et al. *Obstet Gynecol*. 2010 Oct;116(4):827-33.

CDC-Funded Study to Assess Screening Questionnaires During Pregnancy

- **Three-site study that will assess 1,200 pregnant women**
 - Yale, Wayne State (Detroit), Massachusetts General Hospital
- **Step 1: Pregnant women are administered 5 screening questionnaires**
- **Step 2: Participants are assured of confidentiality, asked about comprehensibility and comfort with questions, and invited to provide a urine sample to test for a range of substances**
- **Step 3: Performance characteristics (e.g., sensitivity, specificity) for questionnaires will be compared; multivariable analysis will be used to build a new predictive measure**

Number of Positive Urine Tests by Study Site



Unpublished data

MGH: Massachusetts General Hospital

Cotinine: Predominant metabolite of nicotine, used as a biomarker for exposure to tobacco smoke

THC: Tetrahydrocannabinol (principal psychoactive ingredient in marijuana)

Treatment

- **For pregnant women with opiate addiction, the American Congress of Obstetricians and Gynecologists recommends maintenance therapy**
- **Maintenance therapy includes buprenorphine or methadone**
 - As part of comprehensive treatment, results in fewer obstetric complications
 - In one study, buprenorphine-exposed neonates required 89% less morphine to treat NAS, a 43% shorter hospital stay, and a 58% shorter duration of medical treatment
- **Screening and Brief Intervention and Referral to Treatment (SBIRT) can lead to decreased use of other substances (e.g., nicotine and alcohol)**

Summary

- **We still do not know the best approach to screening for substance use in pregnancy, but comparative research is underway**
- **Both biologic tests and self-report may underestimate the magnitude of the problem**
 - Concerns about legal implications of positive screens or tests
- **Efforts should be made to avoid stigmatization by not focusing on particular racial, ethnic, or socioeconomic populations**
- **Detection of substance use in pregnancy should be coupled with assistance in obtaining treatment**

Using Hospital, State, and Federal Policies to Improve Care to Families Affected by NAS



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U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Improving Outcomes for Women and Infants

- **Responses to the prescription opioid epidemic have often not explicitly included pregnant women and infants**
- **Evidence base for clinicians, hospitals, along with federal and state governments is lacking**
- **Hospitals and states vary greatly in their approaches to women with opioid use disorder and infants with NAS**
- **Coordinated, “system-wide” approaches are needed to optimize outcomes for this vulnerable population**

Hospital Variability in NICU Care

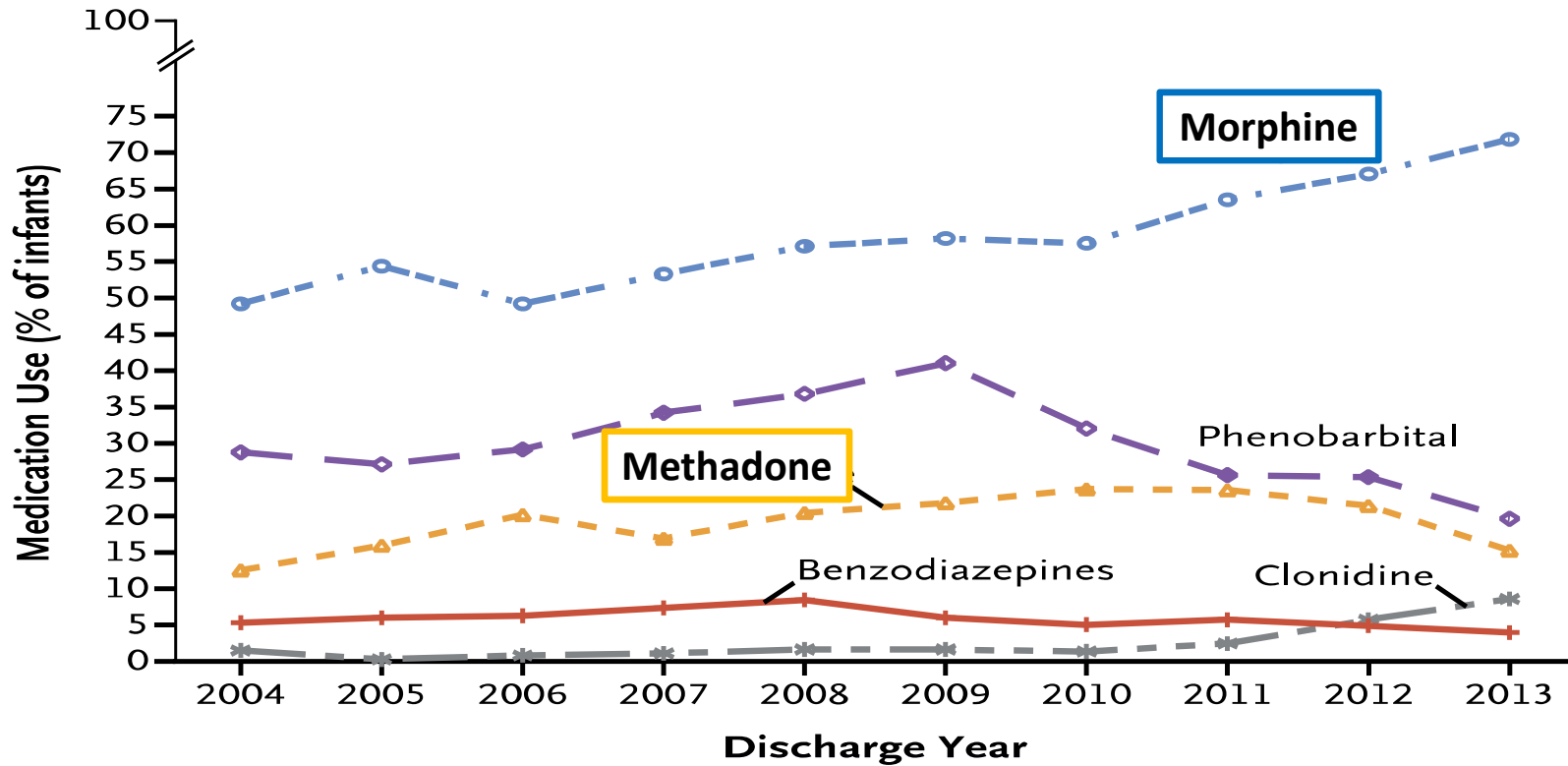
- **NAS now accounts for 50% of NICU hospital days in some hospitals**
- **There is significant inter- and intra-hospital variation in treatment and outcomes for NAS**
- **Recent studies of U.S. children's hospitals indicate:**
 - Two-fold differences in risk-adjusted length of stay
- **Large international 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

NICU: Neonatal Intensive Care Unit

Patrick SW, Kaplan HC, Passarella M, et al. *J Perinatol*. 2014 Nov;34(11):867-72.

Patrick SW, Schumacher RE, Horbar JD, et al. *Pediatrics*. 2016 May;137(5).

Treatment Variation for NAS



Morphine and methadone are the recommended first-line treatment for infants with NAS

Standardizing Care Results in Shorter Treatment Courses and Hospital Stays

➤ Ohio perinatal collaborative, multicenter cohort

- Weaning from opioids according to protocol vs. without a protocol results in shorter length of treatment (17.7 vs. 32.1 days, $p < 0.001$)

➤ Vermont Oxford Network NAS collaborative, 2013–2015

- Participating hospitals, care standardized by protocol or policy development
 - ▢ Shortened length of treatment from 16 days to 15 days ($p = 0.02$)
 - ▢ Shortened length of stay from 21 days to 19 days ($p = 0.002$)
- Hospitals with protocols or policies focused on infant symptom scoring had lowest length of stay
 - ▢ 3.1 days (95%CI -4.9, -1.4)

Hall ES, Wexelblatt SL, Crowley M, et al. *Pediatrics*. 2014 Aug;134(2):e527-34.

Patrick SW, Schumacher RE, Horbar JD, et al. *Pediatrics*. 2016 May;137(5).

State Policies

➤ **States vary in their approach to substance exposure in pregnancy**

- One state allowed for criminal prosecution (Tennessee)
- 18 states consider it child abuse
- 12 states prioritize pregnant women for treatment

➤ **Child Abuse Prevention and Treatment Act**

- Passed in 1974, reauthorized in 2010
- States vary in implementation

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 20th week → No prosecution, no child removal just for history of drug misuse

➤ **Public Chapter 820, 2014**

- A woman can be charged with a misdemeanor if she illegally uses narcotics during pregnancy and if the baby is harmed as a result (e.g., neonatal abstinence syndrome)
 - Law expired in July 2016

➤ **Punitive approaches to substance use in pregnancy are ineffective and may lead to women avoiding medical care**

Federal Policy

EPIDEMIC: RESPONDING TO AMERICA'S PRESCRIPTION DRUG ABUSE CRISIS

2011



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 including opioids

➤ Monitoring

- Every state recommended to have a Prescription Drug Monitoring Program (PDMP)
- Work towards sharing and exchanging prescribing data between states (interoperability)
- Evidence suggests PDMP implementation associated with reduction in overdose deaths
 - More frequent data updates, more types of controlled drugs monitored yield greater reductions

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
 - Drug Enforcement Agency National Take-Back Initiative
 - 2014 rule to enable take back

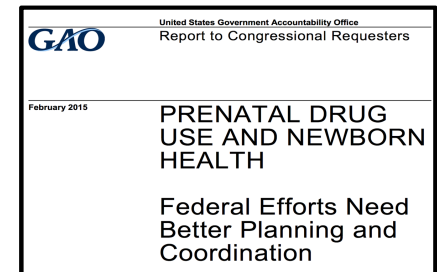


➤ Enforcement

- Provide law enforcement with the tools necessary to eliminate improper prescribing practices and stop “pill mills”

Government Accountability Office: Prenatal Opioid Use and NAS

- **NIH research funding from 2008–2013 was \$21.6 million**
 - 2012 costs for hospital charges alone: \$1.5 billion
- **14 federal programs provide direct services**
- **Coordination of HHS-wide efforts is needed**
 - “...there is a risk that federal efforts may be duplicated, overlapping, or fragmented.”



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
- National All Schedules Prescription Electronic Reporting (NASPER) Reauthorization
- 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**

Additional Federal Policy Efforts

➤ **Food and Drug Administration (FDA)**

- 2013 ER/LA opioids black box warning
- 2016 IR opioids black box warning

Black-box warning: appears on a prescription drug's label, designed to call attention to **serious** or **life-threatening** risks

➤ **Substance Abuse and Mental Health Services Administration (SAMHSA)**

- Guidelines for management of opioid use disorder in pregnancy and infants with NAS released this month

Public Health Approach to NAS

➤ Primary Prevention

- Access to contraception
- Responsible prescribing
- Tobacco cessation
 - Tobacco combined with opioid use increases risk of NAS

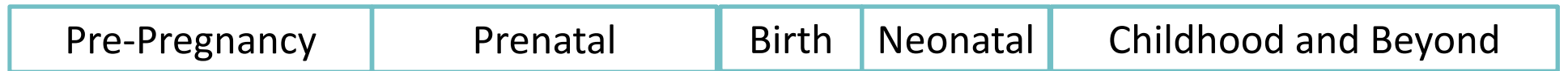
➤ Secondary Prevention

- Screening, Brief Intervention, and Referral to Treatment

➤ Tertiary Prevention

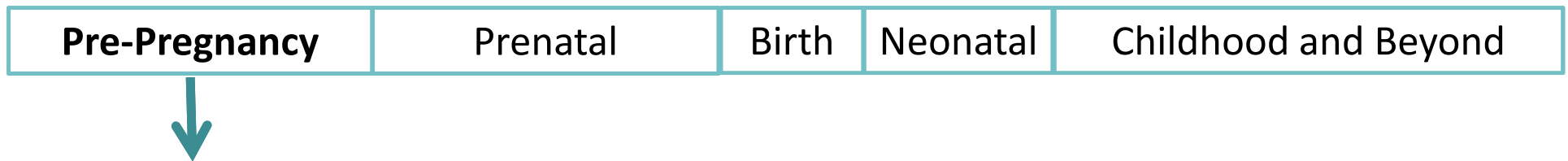
- Decrease variability in treatment
- Prevent readmission

Moving Towards NAS Prevention



NAS Treatment Focuses on Birth

NAS Prevention Across the Life Course

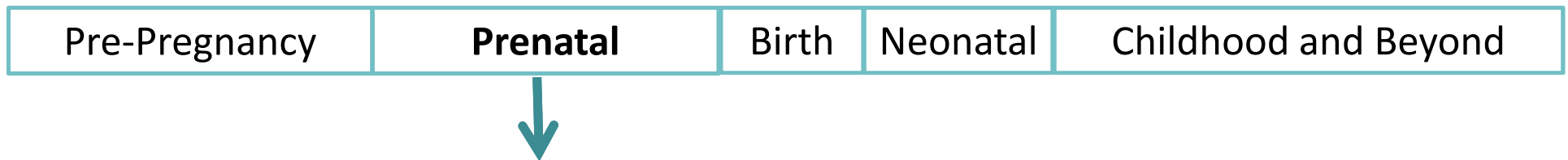


➤ **Public health systems to prevent opioid dependency**

- Prescription drug monitoring programs
- Access to treatment

➤ **Decrease proportion of unplanned pregnancies among women who abuse opioids (86%)**

NAS Prevention Across the Life Course



- **Identify substance use disorders in pregnancy**
- **Decrease overprescribing in pregnancy**
- **Evaluate co-morbidities in pregnancy (e.g., infectious, psychiatric)**
 - Substance use may increase risk for hepatitis C
- **Identify targets to reduce risk (harm reduction) for mother and infant**

NAS Prevention Across the Life Course



- **Improve identification of at-risk infants**
- **Decrease transfers to tertiary care facilities, improve and sustain treatment in the community**
- **Improve care standardization and decrease variability**

NAS Prevention Across the Life Course




- **Decrease readmission risk**
- **Understand long-term risks**
- **Find modifiable risks**
 - Long medication tapers
 - Risk of developmental delay

Summary

- **Clinical and policy approaches to opioid use disorder and NAS have been variable and not always supported by evidence**
- **Progress is being made at all levels of government and the health care system in understanding opioid use disorder and NAS**
- **Future efforts to improve care for women with opioid use disorder and infants with NAS should be grounded in public health principles**

Turn the Tide: Surgeon General's Call to End the Opioid Crisis



1783
have taken the pledge

BE THE SOLUTION. JOIN THE MOVEMENT.

join now

turnthetiderx.org

CDC PUBLIC HEALTH GRAND ROUNDS

Primary Prevention and Public Health Strategies to Prevent Neonatal Abstinence Syndrome



August 16, 2016



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention