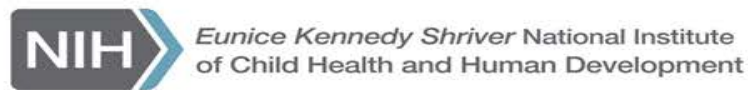


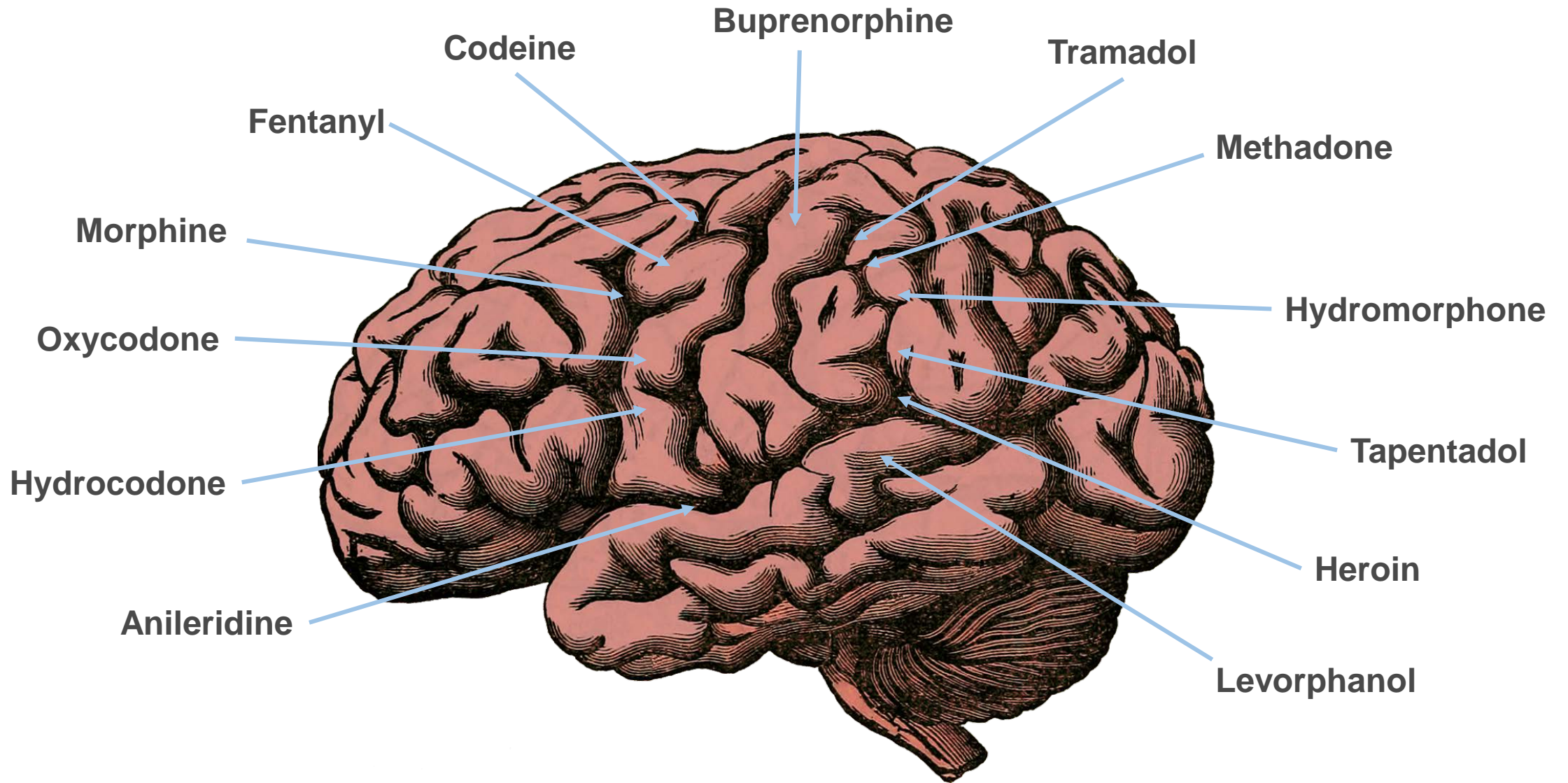
Neonatal Opioid Withdrawal Syndrome: The NIH Response

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National Institutes of Health - Largest funder of biomedical research in the world
Eunice Kennedy Shriver National Institute of Child Health and Human Development
(NICHD) one of 27 Institutes and Centers



Background:

What is NOWs?

- Updated nomenclature for “Neonatal Abstinence Syndrome,” which was first identified in 1970s
- Refers to signs and symptoms in newborns prenatally exposed to opioids
- Characterized by irritability, tremors, feeding issues, vomiting, diarrhea, sweating, seizures, inability to be soothed

**NOWs:
Geometric
Growth
Nationwide**

- Opioid use has quadrupled over the last decade
- 259 million prescriptions for opioids in 2012
- Every 3 minutes a woman seeks emergency care for prescription opioid misuse
- Deaths involving synthetic opioids (mostly fentanyl) have increased from 3,000 to 20,000 in just three years



Health and Fiscal Impact of Opioid Use During Pregnancy

- On average, women take between 3 – 5 prescription medications during pregnancy
- Increased prevalence of opioid use during pregnancy ≥ 5 times increase in NOWs
- In 2012, nearly 22,000 infants were born with NOWs in U.S.
- Nationwide costs: \$1.5 Billion in hospital charges for treating infants with NOWs
- In 2015, one Wisconsin county spent $>$ \$1 million (out of a \$9 million budget) on child welfare placements, largely as a result of parental opioid addiction



Prevention of NOWs Starts With Prenatal Care

- Many women using opioids receive little or no prenatal care
 - Those who do are reluctant to disclose substance use
- Screen pregnant women with opioid use disorder at intervals throughout pregnancy to optimize care
- Medication-assisted therapy is the standard of care
 - Methadone treatment: improved compliance with obstetric care, higher birth weights, and lower preterm birth and infant mortality rates
 - Buprenorphine treatment: decreased risk of overdose and improved neonatal outcomes
- Interest has increased in medically supervised withdrawal, but unclear whether this approach safe for the pregnant woman and her fetus



Infants Exposed to Opioids

- Need to think about babies differently from adults
 - They generally do not die as a result of exposure
 - Most babies are born in the hospital and are resuscitated if they do not breathe
 - Not all newborns exposed to opioids develop significant signs of withdrawal right away
- In newborns prenatally exposed to methadone, signs of NOWs appear within 3-5 days of birth
 - Often after discharge from hospital
- Environmental factors (e.g., cigarette smoke) may increase incidence and severity of NOWs





What Can We Do For Infants With NOWs?

- Best managed in a calm environment
 - Where to treat?
 - Newborn intensive care unit, special setting, or home?
- Encourage breastfeeding
- Up to 80% require pharmacologic interventions (morphine or methadone)
 - When maximum dose reached, second line medication added
- Evaluation by social services
 - Can infant go home with mother or does infant require placement in foster home?



Breastfeeding

- Breastfeeding associated with decreased severity of NOWs, enhanced maternal-child bonding
- Breastfed infants less likely to need pharmacologic treatment compared to formula-fed infants
- Rates of breastfeeding are low – about half of women on methadone stop within 6 days of delivery





What is NIH Doing in Response to the Public Health Crisis of NOWs?



Building Expertise

- NICHD - Previously funded grants
 - Testing a drug treatment in pregnant women and their newborns to reduce the incidence or severity of NOWs (July 2012-May 2018)
 - Studies to determine more precise dosing of buprenorphine in pregnant women, given physiological changes (started in July 2015)
- April 2016 - NICHD hosted a scientific workshop to identify research gaps for screening and management of opioid misuse and NOWs. Published in *Obstetrics and Gynecology* July 2017.
- May 2016 - NIH/NIDA announced a new research effort to reduce the time it takes to improve or develop new medications to treat pain, addiction, and reverse overdoses.



Immediate Research Needs

- **Basic:** Identify neurodevelopmental consequences of *in utero* exposure to opioids;
- **Obstetric:** Determine optimal screening, treatment, and care during pregnancy;
- **Neonatal:** Develop a new screening tool for neurobehavioral assessment of newborn's functioning, identify additional and optimal approaches to treatment;
- **Long-term:** Study outcomes of opioid exposure and treatment on brain development, cognitive function and overall child health.



New Funding Opportunity: Opioid Use Disorder in Pregnancy (RFA-HD-18-036)

Research Topics:

- Clinical studies of maternal medically-supervised opioid withdrawal examining maternal, fetal, and neonatal outcomes
- Pharmacokinetic and pharmacodynamic studies of medications used to treat opioid use disorder in pregnant and/or post-partum women
- Pharmacogenomic and other studies of genetic or epigenetic factors associated with the effects of opioid use during pregnancy on fetal and neonatal outcomes



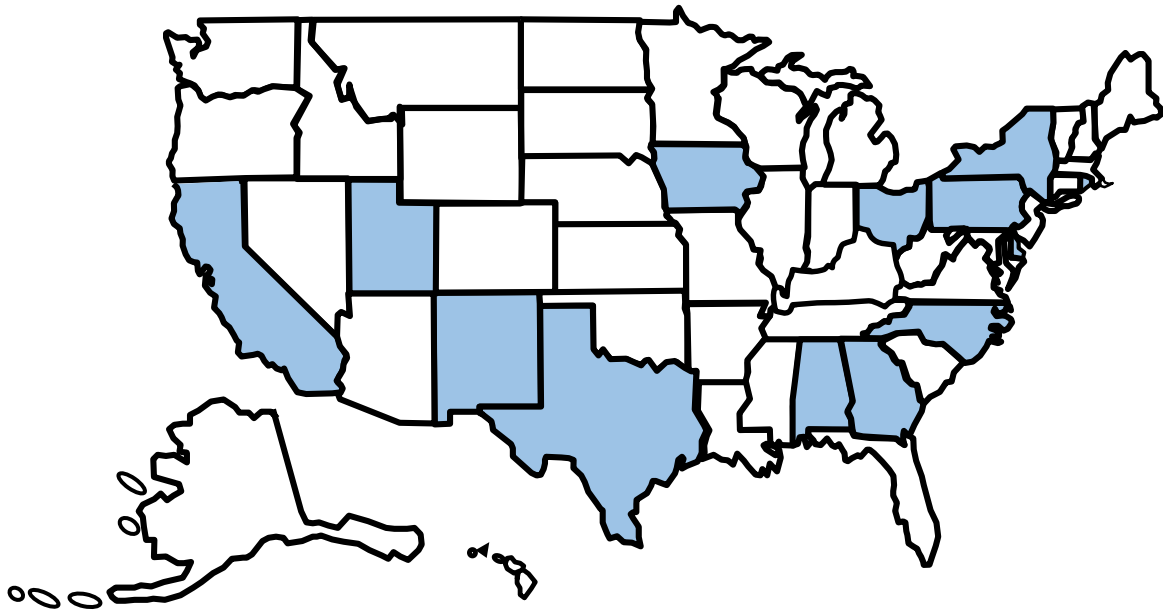
ACT NOW: Advancing Clinical Trials in NOWs

- Initial funding received in August from Director Collins' Discretionary Fund
- Partnership between NICHD/ECHO/NIDA
- FY 2018 Goals: (1) Develop a survey to obtain information on the sites, local practices, demographics, and volume of patients affected with NOWs
- (2) Develop and conduct an observational study to obtain prospective data to inform development of a clinical trial
- (3) Pilot a common protocol to generate evidence to inform best practice



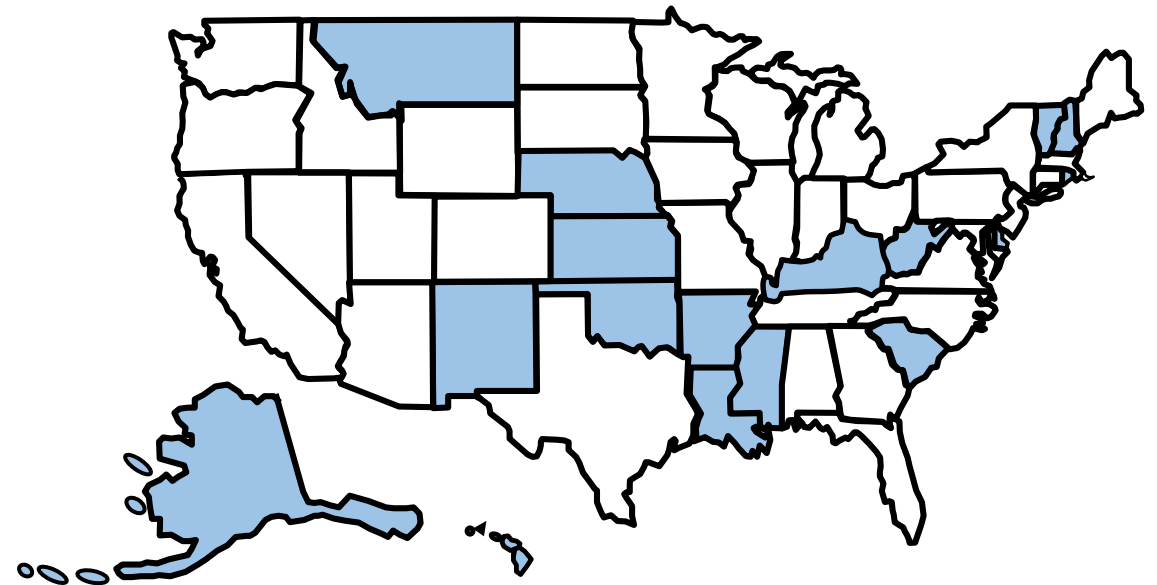


Neonatal Research Network Centers (2016-2021)



- Started in 1986
- 15 sites, mainly urban
- Sites do not necessarily have high prevalence of NOWs

IDeA States Pediatric Clinical Trials Network



- Started in 2016
- 17 sites, many are rural
- Sites overlap with areas of high prevalence of NOWs



21st Century Cures Act: **Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)**

- NICHD is lead institute, first of three meetings held in August 2017
- Task Force report and recommendations due to HHS Secretary and Congress by September 2018
- Opportunities for scientific and public input on medications and other therapies used by pregnant and lactating women
- Prenatal and newborn effects included
- New attention to an under-studied issue



NICHD Pregnancy and Lactation Literature Analysis 2006-2017: Results for Pregnancy

- RCTs rare in almost all areas
- Exceptions:
 - Gestational diabetes
 - Hypertension
 - Preterm labor
 - Labor pain medication
 - Opioids and tobacco

	Condition	Basic	PK/PD	Pop/DB	RCT
Hypertension	Hypertension	127	9	18	40
Mental Health	Anxiety	16	0	3	2
	Bipolar	1	0	1	0
	Depression	21	4	21	4
	Schizophrenia	11	0	1	0
Pain	Labor Pain	5	0	7	49
	Headache/migraine	0	0	5	1
Preterm labor	Preterm labor	152	21	35	169
Substance Abuse	Alcohol	26	0	0	0
	Cocaine	6	0	1	0
	Meth/amph	10	3	1	0
	Opioids	22	3	9	25
	Tobacco	22	3	16	27



Take Home Messages

- NOWs is a growing public health crisis
- Babies have different treatment needs than adults
- Most research at present focuses on short-term treatment
- Long-term effects of opioid exposure to developing brains are largely unknown
- Multi-disciplinary partnerships within and outside NIH are needed
- NIH's role is to perform research that generates the evidence upon which professional groups can make recommendations



Questions?