Tackling the Opioid Crisis

effects on the neonate

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Upon completion of this activity, participants will be better able to ….

- Identify newborns at risk for NAS/NOWS
- Recognize the symptoms of NAS and discuss treatment options
- Describe potential long-term sequelae of fetal exposure to opioids

Classification

- Opioid
  - Broad term – includes opiates
  - Includes any substance, natural or synthetic, that binds to opioid receptors
- Naturally occurring, from opium ("opiates")
  - morphine, codeine
  - Heroin
- Synthetic, bind same receptors
  - fentanyl, methadone
- Semi-synthetic, chemical modification of natural
  - oxycodone, hydrocodone

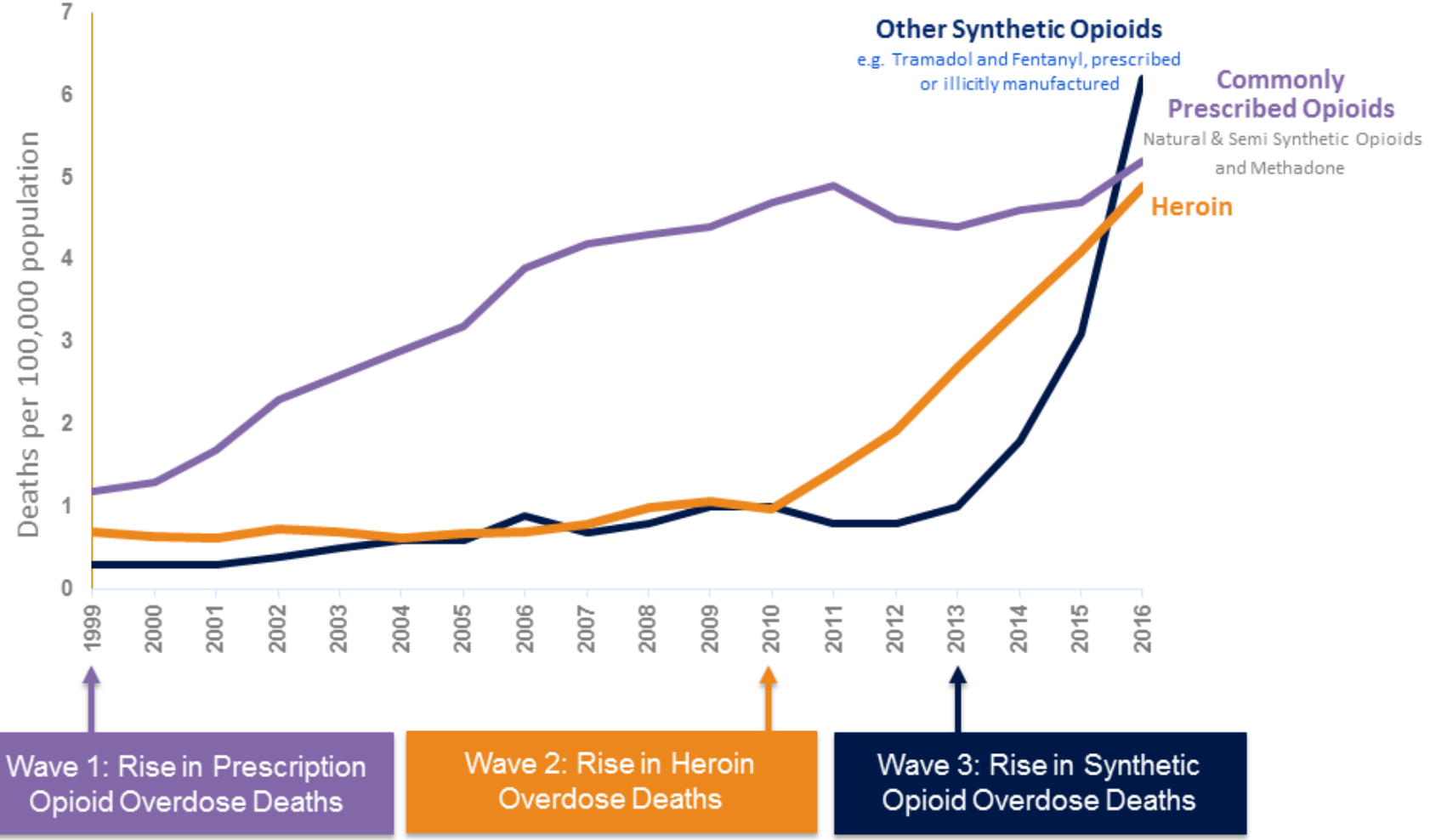
The Opioid crisis

- October 2017: HHS declared a public health emergency

- Announced 5-Point strategy to combat the opioid crisis
  - Improve access to prevention, treatment, and recovery support services
  - Target the availability and distribution of overdose-reversing drugs
  - Strengthen public health data reporting and collection
  - Support cutting-edge research on addiction and pain
  - Advance the practice of pain management

https://www.hhs.gov/opioids

3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

52,404 Americans died from drug overdoses in 2015, and preliminary numbers indicate at least 64,000 died in 2016.

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Opioid Epidemic Boosts The Death Rate Among US Millennials

By Paul Gaita 01/08/18

According to CDC data, the death rate rose 19% for adults between the ages of 25-34 over a two-year-period.

Federal officials reported in December 2017 that drug overdoses have contributed to a second consecutive drop in life expectancy among U.S. adults, and now the opioid epidemic in America has been credited with another alarming statistic: the Centers for Disease Control and Prevention (CDC) has found that the death rate among "millennials"—which for the purposes of the report, is attributed to adults between the ages of 25 and 34—rose 19% between 2014 and 2016, the highest such percentage in more than two decades.

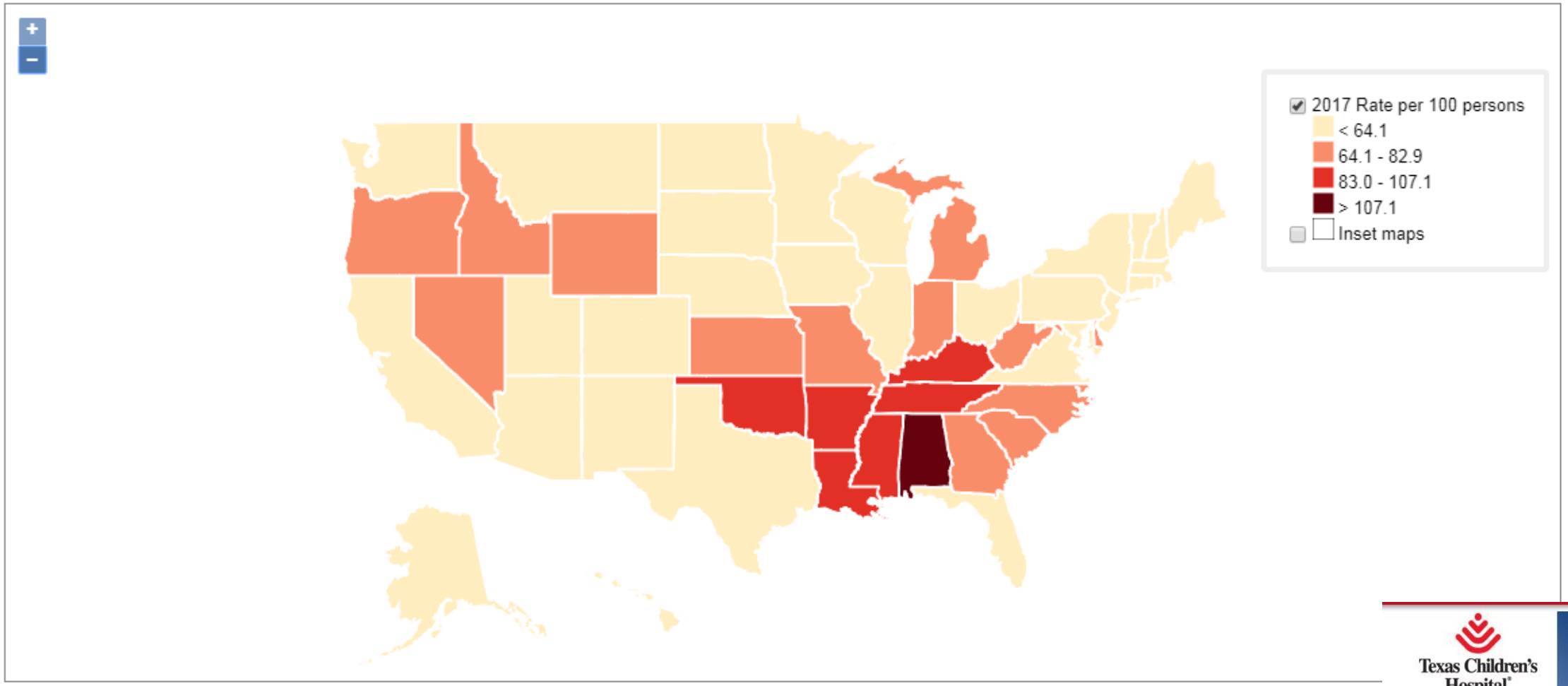
Coverage of the CDC report on the digital news outlet *Quartz* has linked the figures to an increase in drug overdose deaths among that demographic, which rose from 23 out of every 100,000 Americans in 2014 to nearly 35 in 2016.

Opioid Overdose

U.S. State Prescribing Rates, 2017

U.S. State Prescribing Rates, 2016

U.S. Prescribing Rate Maps



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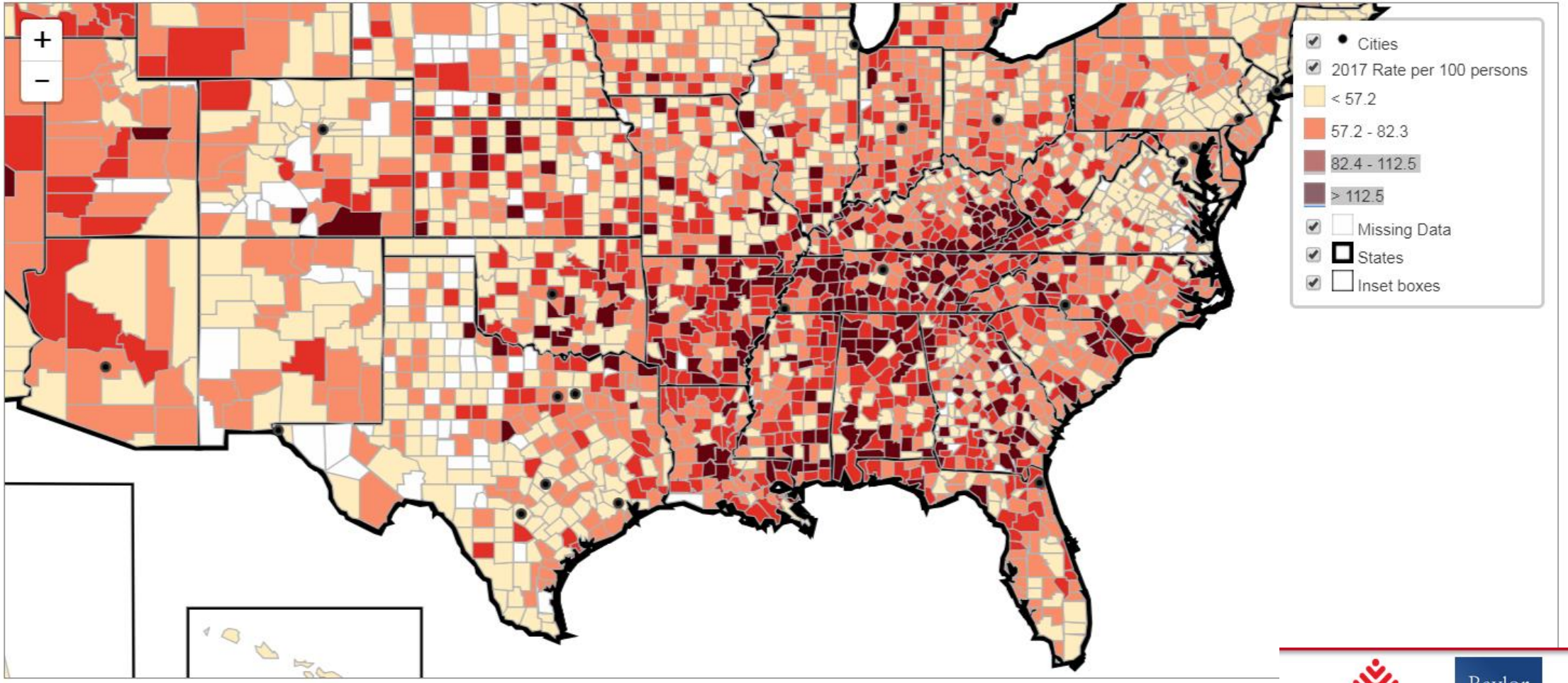
U.S. County Prescribing Rates, 2017

U.S. County Prescribing Rates, 2016

U.S. Prescribing Rate Maps



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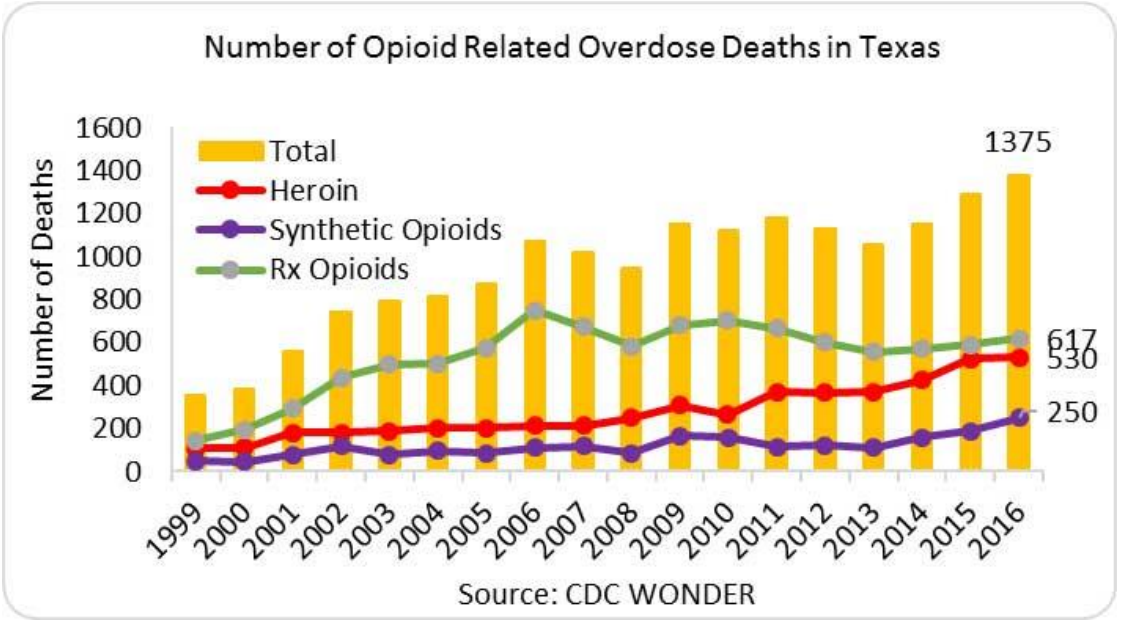
Texas

- Drug overdose death rate: 44th in U.S.
- Opioid prescription rate: 33rd in U.S.



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Opioid use – women of childbearing age

Prescriptions filled , ages 15 –44 years (2008-2012):

- 39% Medicaid-enrolled women (age 40-44 more likely)
- 28% privately insured women (age 30-34 more likely)
- Most common: hydrocodone, codeine, oxycodone

CDC MMWR report 2015

Every 3 minutes a women seeks ER care for opioid misuse

- Doesn't include illicit drug use – heroin
- 2015: 600,000 Americans report heroin use

CDC MMWR report 2017

Pregnancy

- May be only mother's only contact with a health care provider
- Screening during prenatal visit
  - Fear of legal ramifications, child custody issues, etc.
  - With what tool, at what time ?
- Associated morbidities:
  - IUGR
  - Placental insufficiency
  - PROM
  - PPH
  - Fetal mortality

Texas

- **4th** highest birth *rate* in U.S.
- Medicaid pays for **> ½**
- 2010-2015: NAS cases increased by 75%
- Highest NAS cases: Bexar County
  - Mommies Program (DSHS grant) – toolkit
  - NAS Residential Treatment Program

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Pregnancy

- Opioid use disorder during pregnancy: ~ 4/1000 deliveries
  - Varies by state
  - 0.7/1000 (DC) – 48/1000 (Vermont)
- Complete abstinence ideal
  - Withdrawal dangerous for mom and baby (PTL, pregnancy loss, etc)
  - High relapse rates
- Medication-assisted treatment (MAT) recommended
  - Long-acting opioid agonist
  - Steady levels – reduce maternal craving

Maintenance treatment

- Methadone
  - Widely used since 1970s
  - Long-acting, often requires increased dosing as pregnancy progresses
  - Can only be dispensed through an opioid treatment program certified by SAMHSA.
  - Lower drop out rates
- Buprenorphine
  - Partial agonist, binds with higher affinity, lower activity
  - Ceiling dose of 32 mg (may not be high enough)
  - Prescriptions are easier to obtain (DATA)
  - Higher drop out rates

PREGNANCY:

Methadone and Buprenorphine

Some women are surprised to learn they got pregnant while using heroin, Oxycontin, Percocet or other pain medications that can be misused (known as opioid drugs). You, along with family and friends, may worry about your drug use and if it could affect your baby.

Some women may want to "detox" as a way to stop using heroin or pain medicines. Unfortunately, studies have shown that 8 out of 10 women return to drug use by a month after "detox." Therefore, most doctors treat opioid misuse in pregnant women with either methadone or buprenorphine. These are long-acting opioid medications that are associated with improved outcomes in pregnancy.

HOW SAFE IS IT TO TAKE METHADONE OR BUPRENORPHINE (SUBUTEX®) DURING PREGNANCY?

- In the right doses, both methadone and buprenorphine stop withdrawal, reduce craving, and block effects of other opioids.
- Treatment with either methadone or buprenorphine makes it more likely that the baby will grow normally and not come too early.
- Based on many years of research studies, neither medicine has been associated with birth defects.
- Babies born to women who are addicted to heroin or prescription opioids can have temporary withdrawal or abstinence symptoms in the baby (Neonatal Abstinence Syndrome or NAS). These withdrawal symptoms (NAS) also can occur in babies whose mothers take methadone or buprenorphine
- Talk with your doctor about the benefits versus the risks of medication treatment along with the risks of not taking medication treatment.

IS METHADONE OR BUPRENORPHINE A BETTER MEDICATION FOR ME IN PREGNANCY?

- A pregnant woman and her doctor should discuss both methadone and buprenorphine. The choice may be limited by which medication is available in your community.
- If a woman is already stable on methadone or buprenorphine and she becomes pregnant, doctors usually advise her to stay on the same medication.

HOW CAN I GET STARTED ON METHADONE OR BUPRENORPHINE?

- Depending where you live, there may be a special program that offers care to pregnant women who need methadone or buprenorphine. These programs can offer prenatal care and substance use counseling along with your medication.
- Methadone may only be given out by specialized clinics while buprenorphine may also be available from your primary care physician or obstetrician if they have received special training.
- Some women will prefer or benefit from starting these medications while in a residential (inpatient) treatment facility.

WHAT IS THE BEST DOSE OF METHADONE OR BUPRENORPHINE DURING AND AFTER PREGNANCY?

There is no "best" dose of either medication in pregnancy. Every woman should take the dose of methadone or buprenorphine that is right for her.

- The "right" dose will prevent withdrawal symptoms without making you too tired.
- The right dose depends on how your body processes the medications.
- In pregnancy, you process these medications more quickly, especially in the last several months and this affects what dose you need.
- The dose of methadone usually needs to increase with pregnancy – especially in the third trimester and you may need to take methadone more than once a day.
- There is less known about buprenorphine dose changes in pregnancy, but increases may be necessary.
- The dose does not seem to determine how much NAS a baby will have.
- After delivery, the methadone or buprenorphine dose may remain the same or may decrease as your body returns to its non-pregnant state. This can take up to a few months after delivery.

Your dose should be reduced if it begins to cause sedation. Be sure to discuss whether you are feeling too sleepy with your doctors, nurses, and counselors. *For further information, please see brochure Childbirth, Breastfeeding and Infant Care; Methadone and Buprenorphine.*

Methadone and buprenorphine - pregnancy

- Decreases illicit drug use
- Improves compliance with prenatal care
- Higher birth weights
- Cochrane review 2013:
  - Methadone: decreased number of drop outs
  - Buprenorphine: less severe neonatal withdrawal
  - Neither deemed superior to the other
- Still at risk for neonatal withdrawal

Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review

Jennifer N. Lind, PharmD, MPH,[a,b] Julia D. Interrante, MPH,[a,c] Elizabeth C. Ailes, PhD, MPH,[a] Suzanne M. Gilboa, PhD,[a] Sara Khan, MSPH,[a,d,e] Meghan T. Frey, MA, MPH,[a] April L. Dawson, MPH,[a] Margaret A. Honein, PhD, MPH,[a] Nicole F. Dowling, PhD,[a] Hilda Razzaghi, PhD, MSPH,[a,b] Andreea A. Creanga, MD, PhD,[f,g] Cheryl S. Broussard, PhD[a]

- Systematic review: 1946-2016, 68 studies met inclusion criteria
- Case control studies (10)
  - associations w/ oral clefts and VSDs/ASDs – 3 studies
  - Spina bifida – 2 studies
- Cohort studies (7)
  - clubfoot - 6 studies
- ?hydrocephaly, glaucoma, gastroschisis

PEDIATRICS Volume 139, number 6, June 2017:e20164131

Neonatal abstinence syndrome (NAS) or Neonatal Opioid Withdrawal Syndrome (NOWS)

- Drug withdrawal syndrome
  - NAS – all substances (meth, cocaine, etc)
  - NOWS – specific to opioids
- Variable presentation, several systems can be affected:
  - Central nervous system
  - Autonomic nervous system
  - Respiratory
  - Gastrointestinal
- Diagnosis can be difficult in polysubstance use

NAS (NOWS)

- Central nervous system
  - Tremors, irritability, sleep disturbance, hypertonia, hyperreflexia
  - Seizures
- Autonomic nervous system
  - Hyperthermia, sneezing, yawning
- Respiratory
  - Tachypnea
- Gastrointestinal
  - Loose stools, poor feeding, vomiting, poor weight gain

Timing of withdrawal

- Short acting: 24 hours (fentanyl, heroin)
- Long acting: 24-48 hrs, can take up to 7-10 days
  - Methadone/buprenorphine: 48-72 hours
- Minimum 5 day stay to observe

NAS (NOWS) numbers

- 5-fold increase over past decade
- Cohort analysis of data from 299 U.S. NICUs :
  - Increase in admissions for NAS: **7/1000 to 27/1000**
  - Increase in median length of stay: **13 day to 19 days**
  - % increase in NICU days attributable to NAS: **0.6% to 4%**
- Baby born every 15-25 minutes with signs of opioid withdrawal

*Patrick SW, et al. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009-2012. J Perinatol 2015;35(08):667
**Tolia VN, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. N Engl J Med 2015;372(22):2118-2126.

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NAS

- Withdrawal symptoms
  - 55 – 94% of exposed babies (any)
  - 50% of babies born to mothers taking methadone or buprenorphine
  - Co-exposure to psychotropic med(s) close to delivery (benzos, SSRIs)
    - Single med: 30-60% increase
    - Two or more: doubles the risk
  - Nicotine: higher Rx rates, higher total dose of meds
  - Genetic factors

Wachman, et al. , 2011
Jansson, et.al 2012

Diagnosis

- Early recognition important
  - prevent premature hospital discharge
- Maternal testing - usually urine
  - Previous positive drug test
  - Placental abruption
  - Idiopathic preterm labor
  - Idiopathic fetal growth restriction
  - Frequent requests for prescription drugs of abuse
  - Noncompliance with prenatal care
  - Unexplained fetal demise
  - Methadone / buprenorphine compliance

Diagnosis

- Testing baby
  - Urine – few days prior to delivery
  - Meconium - back to 20 weeks
    - 2nd and 3rd trimester – won't reflect abstinence closer to delivery
    - Often a send-out lab ; ideally collect before first feed
    - Mec stained fluid
  - Umbilical cord – back to 20 weeks
    - 2nd and 3rd trimester exposures
    - Sample immediately available, allowing quicker results
    - Avoids drugs administered to baby after birth
    - Performs as well as meconium*

*Montgomery, et al. Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium. J Perinatol. 2006 Jan 1;26(1):11-4
*Palmer, et al. Evaluating a switch from meconium to umbilical cord tissue for newborn drug testing: a retrospective study at an academic medical center. Clin Biochem. 2017;50:255-261

NAS Diagnosis

- False negative results can occur in neonatal screening
  - URINE
  - MECONIUM
  - UMBILICAL CORD
- Careful history + physical exam
- May require full diagnostic work-up to exclude other causes
  - Sepsis
  - Metabolic derangements (hypocalcemia, hypoglycemia)
  - Hyperthyroidism

Assessment tools/scoring system

- 3 primary scoring tools
  - Systematic, periodic, semi-objective, thorough
    - Lipsitz (1975)
    - Finnegan (1975) Neonatal Abstinence Scoring System (and modified versions)
    - Neonatal Withdrawal Inventory (1998)
  - Lack of evidence to support one tool over another
  - **Finnegan** most widely used
- Limitations
  - Too subjective ?
  - Ages ≥ 37 weeks to 30 days

Premature babies and NAS

- Incidence of NAS lessens as gestational age decreases, possible reasons:
  - Immature CNS
  - Less fat for deposition of drug
  - Reduced total drug exposure time during gestation
  - Decreased receptor sensitivity/development
  - Less ability to express motor dysfunction

Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, AAP. Pediatrics. 2012; 129(2):e540.

Date			time												Comments
Weight			am						pm						
System	Signs and Symptoms	Score	7	8	9	10	11	12	1	2	3	4	5	6	
Central Nervous System Disturbances	Excessive high-pitched (or other) cry (cry face)	2													
	Continuous high-pitched (or other) cry (cry face)	3													
	Sleeps less than 1 hour after feeding	3													
	Sleeps less than 2 hours after feeding	2													
	Sleeps less than 3 hours after feeding	1													
	Hyperactive moro reflex	2													
	Markedly hyperactive moro reflex	3													
	Mild tremors disturbed	1													
	Moderate-severe tremors disturbed	2													
	Mild tremors undisturbed	3													
	Moderate-severe tremors undisturbed	4													
	Increased muscle tone	2													
	Excoriation (specific area)	1													
	Myoclonic jerks	3													
	Generalized convulsions	5													
Metabolic, Vasomotor, & Respiratory Disturbances	Sweating	1													
	Fever less than 101 (99–100.8 F / 37.2–38.2 C)	1													
	Fever greater than 101 (38.4 C and higher)	2													
	Frequent yawning (greater than 3–4 times / interval)	1													
	Mottling	1													
	Nasal stuffiness	1													
	Sneezing (greater than 3–4 times / interval)	1													
	Nasal flaring	2													
	Respiratory rate greater than 60 / min	1													
	Respiratory rate greater than 60 / min with retractions	2													
Gastrointestinal Disturbances	Excessive sucking	1													
	Poor feeding	2													
	Regurgitation	2													
	Projectile vomiting	3													
	Loose stools	2													
	Watery stools	3													
	Total score every 2 to 4 hours														
	Signature of scorer(s)														

- 31 items
- Score every 3-4 hours
- Score every 2 hours if ≥ 8
- Pharmacologic intervention if score **≥ 8** x **3** consecutive scorings
- Developed for term babies

Modified from Finnegan LP, Kaltenbach K. The assessment and management of neonatal abstinence syndrome. In Hoekelman RA. Nelson N, editors: Primary pediatric care, ed 3, St. Louis, 1992, Mosby.

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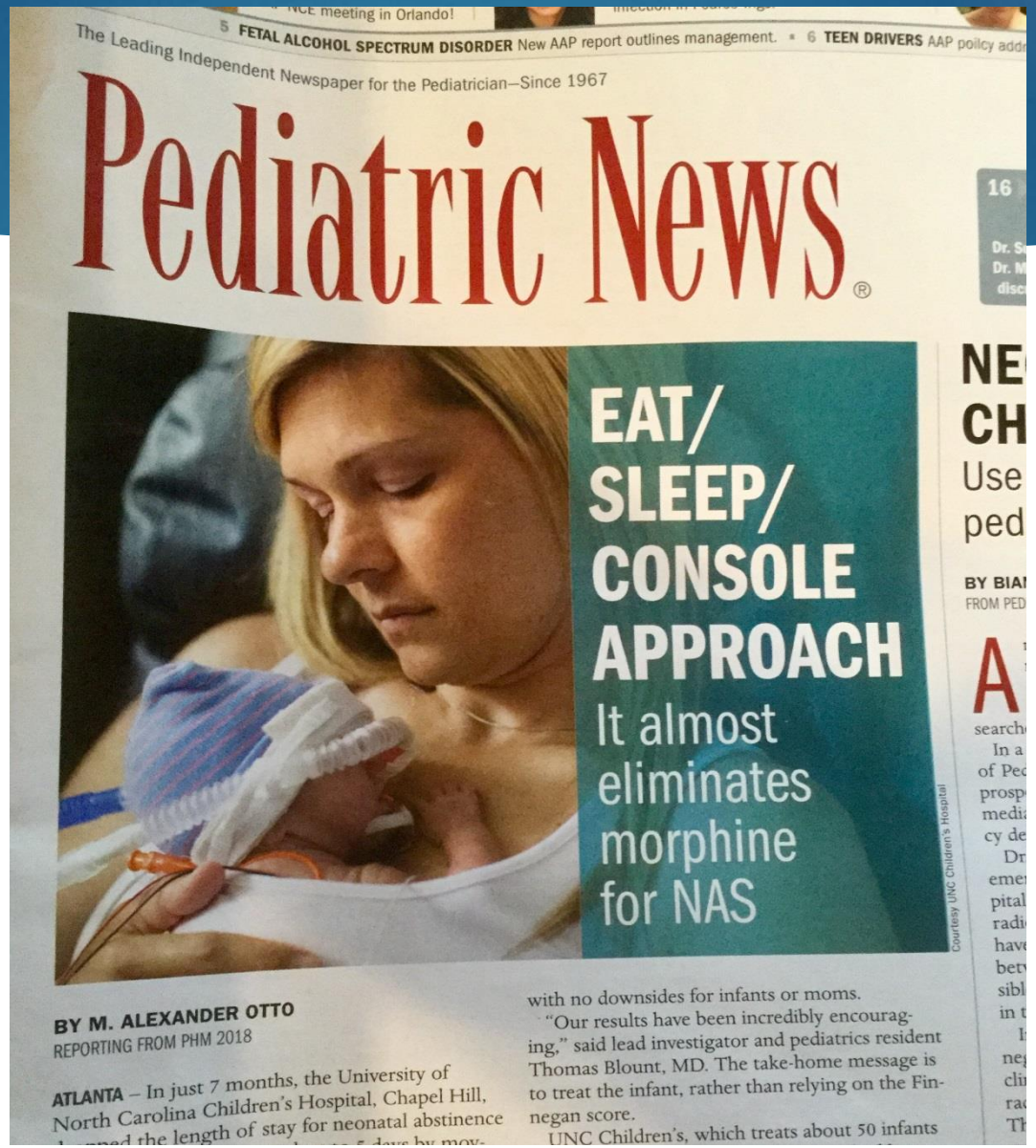
Treatment

Non-pharmacological/ supportive

- Always first line
  - Grossman, et al. 2017; no meds or increase in meds if able to:
    - **Eat**: breast feed effectively or take ≥ 1ounce every feed
    - **Sleep**: undisturbed x at least 1 hour
    - **Console**: within 10 minutes
  - Methadone exposed infants treated with morphine decreased from 98% to 14%
  - Decreased ALOS
  - Other centers adopting
  - Long term safety/efficacy not known



NCE meeting in Orlando!

5 **FETAL ALCOHOL SPECTRUM DISORDER** New AAP report outlines management. ▪ 6 **TEEN DRIVERS** AAP policy add

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Dr. S
Dr. M
disc

Courtesy UNC Children's Hospital

EAT/ SLEEP/ CONSOLE APPROACH

It almost eliminates morphine for NAS

BY M. ALEXANDER OTTO
REPORTING FROM PHM 2018

ATLANTA – In just 7 months, the University of North Carolina Children's Hospital, Chapel Hill, [illegible] the length of stay for neonatal abstinence [illegible] 5 days by mov-

with no downsides for infants or moms.

"Our results have been incredibly encouraging," said lead investigator and pediatrics resident Thomas Blount, MD. The take-home message is to treat the infant, rather than relying on the Finnegan score.

UNC Children's, which treats about 50 infants

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NEWS CITIES FOOD & DRINK ACTIVITIES STORI

Care to Cuddle? Neonatal Units Across the Country Are Implementing Cuddle Programs for Drug Addicted Babies

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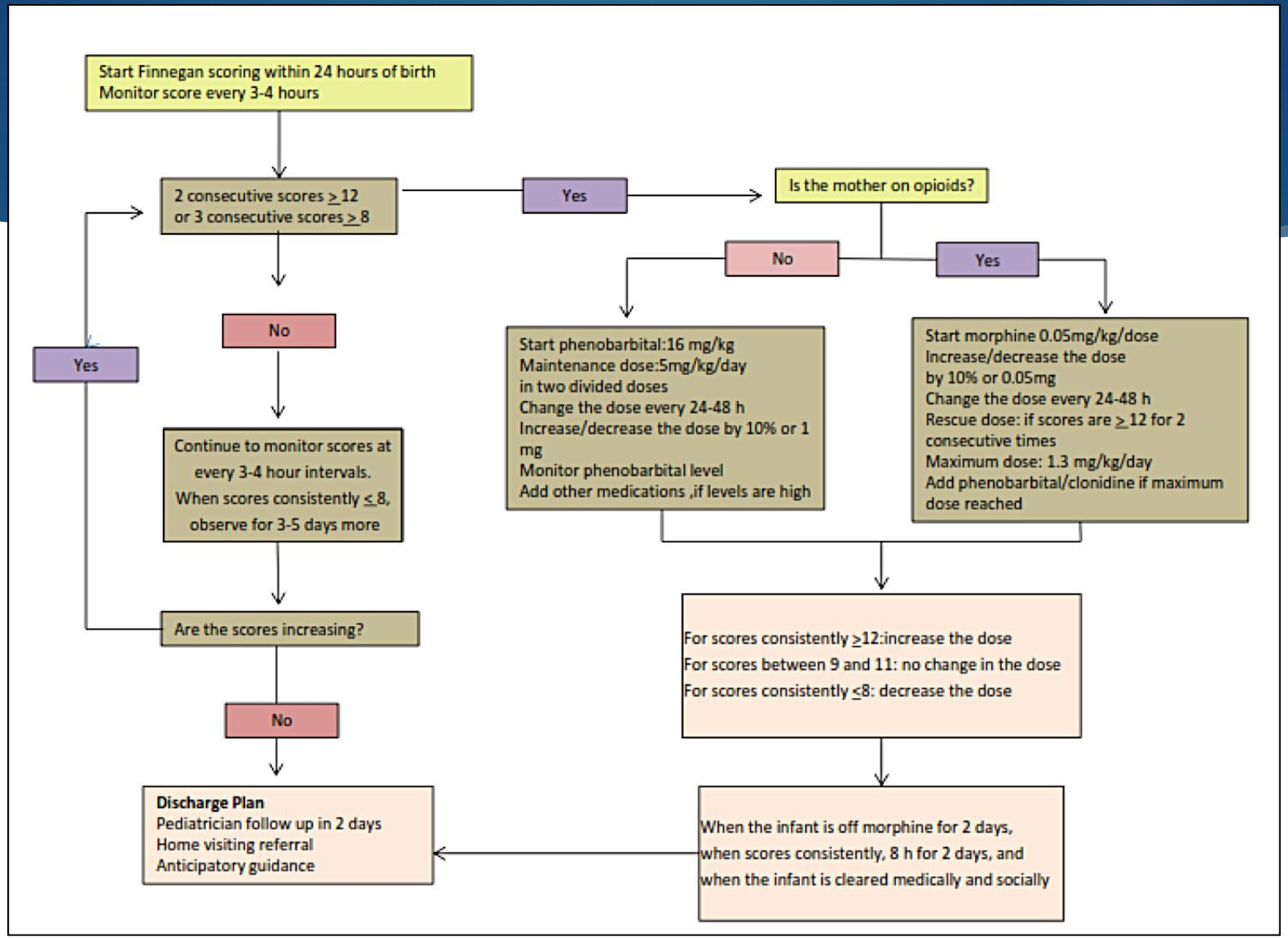
Treatment

Pharmacological

- Significant NAS symptomatology despite supportive care.
- Scoring exceeds predetermined criteria (usually two scores ≥8)
- AAP, Cochrane review:
  - **Morphine**: first line
  - Methadone
  - **Buprenorphine**: may reduce LOS compared to morphine
  - **Phenobarbital**: second line, and non opioid exposure
  - Clonodine?
- No standardized / universal protocol
  - Centers who have adopted a standardized approach have reported better outcomes



A sample hospital management plan for neonates with NAS. Adapted from Kocherlakota (2014)

Pharmacological treatment

TCH

- Morphine
  - start at 0.05 mg/kg/dose q 3 hours
  - Increase by 0.03 mg/kg/dose until symptoms are controlled
  - Wean if at same dose x 48 hour (scores < 8)
  - Wean by 10% (based on original dose) every 24 hours
  - Discontinue when dose < 0.02 mg/kg
- Phenobarbital
  - Adjunctive when morphine dose is > 0.3 mg/kg and scores are still > 8
  - Unable to wean morphine x 3 consecutive days
  - First line drug for non opioid NAS

Treatment

Challenges

- Weaning
- Meconium drug panel is a send out
- High suspicion, negative testing
- Who should breastfeed

- Reported average LOS for NAS: ~ 21 days
  - Reality, if on meds, 4 – 8 weeks

Breastfeeding

- Associated with decrease in incidence and severity of NOWS
  - AAP, ACOG, ABM (protocol #21)
  - Less pharmacological treatment
    - Pharmacological Rx: BF **28.6** days vs **46.7** non BF*
  - Improved maternal-infant attachment
  - Amounts of buprenorphine and methadone transferred to breast milk are small
- Mothers stable on MAT, plan to continue in SA treatment program postpartum
- No illicit drug use (negative drug screen at delivery)
- HIV negative
- Avoid abrupt discontinuation of breastfeeding

*Welle-Strand GK, Skurtveit S, Jansson LM, Bakstad B, Bjarkø L, Ravndal E. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *Acta Paediatr* 2013;**102**(11):1060–6.

Discharge

- Non-pharmacological
  - Observe at least 5 days (TCH guidelines: 5 days)
- Pharmacological
  - Monitored off medications at least 48 hours

- Pediatric medical home identified, follow-up appt made
- Maternal resources, outpatient follow-up identified (SW, psychiatry, CPS, etc)

Long-term effects

- Difficult to accurately assess
  - Polysubstance exposure
    - Nicotine, alcohol: poor outcomes overall
    - Opiates (heroin) + others: loss of brain volume*
  - Higher incidence of IUGR and LBW
  - Poor study retention rates / loss to follow-up
  - Complicated by increased socio-economic risk factors
- Attention deficit disorders
- Behavioral disorders

*Walhovd, et al. 2007 (*Neuroimage*)

Long term effects

- Merhar et al. 2018 (*J Perinatol*), retrospective, cohort study:
  - 87 infants treated for NAS
  - Bayley at 2 years
  - "Children treated for NAS are at risk for lower developmental scores and higher rates of strabismus at age 2 than the general population".
- Nygaard et al. 2015 *(Pediatr Res):*
  - Longitudinal study
  - 72 children, opioid and polysubstance exposure
  - Lower IQ scores on WISC-R at age 8.5 yr

Neonatal Abstinence Syndrome and High School Performance

Ju Lee Oei, MD,[a,b,c] Edward Melhuish, PhD,[d,e,f] Hannah Uebel,[a] Nadin Azzam,[a] Courtney Breen, PhD,[g] Lucinda Burns, PhD,[g] Lisa Hilder, MBBS,[h] Barbara Bajuk, MPH,[i] Mohamed E. Abdel-Latif, MD,[j,k] Meredith Ward, FRACP,[a,b] John M. Feller, FRACP,[a,l] Janet Falconer, CNC,[m] Sara Clews, CNC,[m] John Eastwood, FRACP, PhD,[a,c,n,o,p] Annie Li,[a] Ian M. Wright, FRACP[d,q,r]

Diagnosis code of NAS (ICD-10 P96.1) strongly associated with poor and deteriorating performance on national, standardized achievement test.

- Controlled for GA, socioeconomic status, gender.
- Did not control for maternal age and education.
- Substance(s) used by mother unknown.
- ?pharmacologic vs non-pharmacologic interventions.

Advantage: early identification of at risk children, facilitates earlier intervention

Oei, et al. 2017 *Pediatrics*

Educational Disabilities Among Children Born With Neonatal Abstinence Syndrome

Mary-Margaret A. Fill, MD,[a,b,c] Angela M. Miller, PhD, MSPH,[b] Rachel H. Wilkinson, MPP,[d] Michael D. Warren, MD, MPH,[b] John R. Dunn, DVM, PhD,[b,c] William Schaffner, MD,[c] Timothy F. Jones, MD[b,c]

- Tennessee data 2008-2011
- History of NAS (ICD-9 code 779.5)
- 1,815 children
  - 19.3% referred for evaluation of educational disability (control 13.7%)
  - 15% met criteria for educational disability, eligible for services (control 11.6%)
- Source of exposure unknown

TABLE 2 Univariate Analysis of Special Education Outcomes of Children With a History of NAS ($N = 1815$) and Children Without a History of NAS ($N = 5441$)

Outcome	With NAS, *n* (%)	Without NAS, *n* (%)	*P*
Referred for evaluation	351 (19.3)	745 (13.7)	<.0001
Eligible for services	284 (15.6)	634 (11.6)	<.0001
Autism	6 (0.3)	22 (0.4)	.8
Developmental delay	96 (5.3)	193 (3.5)	.001
Other health impairment	12 (0.7)	27 (0.5)	.5
Specific learning disability	7 (0.4)	16 (0.3)	.6
Speech or language impairment	187 (10.3)	451 (8.3)	.009
Received therapies or services	278 (15.3)	620 (11.4)	<.0001
Accommodations	98 (5.4)	225 (4.1)	.02
Aide or paraprofessional	3 (0.2)	12 (0.2)	.2
Occupational	55 (3.0)	126 (2.3)	.09
Physical	17 (0.9)	54 (1.0)	.8
Speech	255 (14.0)	586 (10.8)	.0002

Fill, et al. September 2018 *Pediatrics*

Pearls

- National crisis, increasing rates in Texas
- Recognize opportunities for intervention
  - Preconception, prenatal
- Prompt diagnosis at birth
  - Diagnosis can be complicated; diagnosis of exclusion
  - No simple lab test to diagnose NAS
- No universal standard of care
  - Standardized protocols shown to allow better outcomes
- Babies with NAS have increased risk of learning and developmental problems
- Multi-disciplinary care of mother and baby after discharge

Questions ?

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