

Neonatal Opioid Withdrawal Syndrome (NOWS)

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Outline

- Definition of Neonatal Opioid Withdrawal Syndrome (NOWS)
- Symptoms of NOWS
- Maternal substances
- Testing of neonates
- Assessment of neonate for NOWS
- Treatment for NOWS
- New approaches



Neonatal Opioid Withdrawal Syndrome (NOWS) aka Neonatal Abstinence Syndrome

A constellation of signs and symptoms of withdrawal in infants who have been exposed to maternal opioids during pregnancy

These symptoms are manifested in CNS irritability, gastrointestinal disturbances, and autonomic instabilities



NOWS Facts

- 55-94% of term infants exposed to narcotics develop NOWS
 - Infants less than 34 weeks gestation rarely develop the typical symptoms of withdrawal seen in term and late preterm infants
 - The early symptoms are mostly autonomic and central nervous system irritability, followed by gastrointestinal dysfunction
-
- American Academy of Pediatrics Committee on Drugs
Pediatrics. Jan 30, 2012

More NOWS Facts

- Seizures occur in 2-10% of infants withdrawing from opioids but may occur more frequently with other drugs
- Over 30% of infants will have abnormal EEGs without overt seizure activity
- Multi-drug exposure may manifest clinically with a biphasic pattern of withdrawal: an exacerbation of symptoms occurring 1-2 weeks after successful treatment of initial symptoms

CNS Signs/Symptoms

- Hypertonia
- Tremors at rest or when disturbed
- High-pitched or prolonged crying
- Extreme irritability and/or restlessness
- Exaggerated Moro reflex
- Sleep disturbances
- Seizures- rarely seen

GI Symptoms

- Frequent loose, watery stools with skin excoriation on buttocks
- Poor or ineffective feeding (chew or bite the nipple)
- Emesis
- Poor weight gain
- Dehydration
- Failure to pass stool in first day or two

Autonomic Symptoms

- Elevated temperature
- Nasal stuffiness
- Sneezing
- Skin mottling
- Tachypnea

Differential Diagnosis

Sepsis

Hypocalcemia

Hypoglycemia

CNS hemorrhage

Meningitis

Perinatal asphyxia

Polycythemia



Hospital Course

- A Day in the Life of an opioid exposed infant
 - Every 3-4 hours: assessment, medication, attempt to po or breastfeed.
 - Many babies cannot po feed, so they are fed by nasogastric tube
 - They spend countless hours in the arms of nurses, parents, or cuddlers. They may have difficulty falling asleep or staying asleep
 - They spend a lot of time in the swing, or in bed with soothing sounds or music playing
 - As they feel better, they begin to sleep between feedings

Opioid Drugs of Addiction

Heroin, methadone, fentanyl

Oxycodone (OxyContin), oxymorphone (Opana),
hydrocodone/acetaminophen (Vicodin)
oxycodone/acetaminophen (Percocet)

Buprenorphine (Subutex or Suboxone),

Morphine, codeine, meperidine, opium

Tramadol



Substances that do not cause NOWS

- Tobacco
- Marijuana
- Cocaine
- Antidepressants, especially SSRIs
 - sertraline (Zoloft), paroxetine (Paxil)
- Amphetamines
- Caffeine
- Alcohol
- Barbiturates
- Benzodiazepines: diazepam (Valium), lorazepam (Ativan)
alprazolam (Xanax)

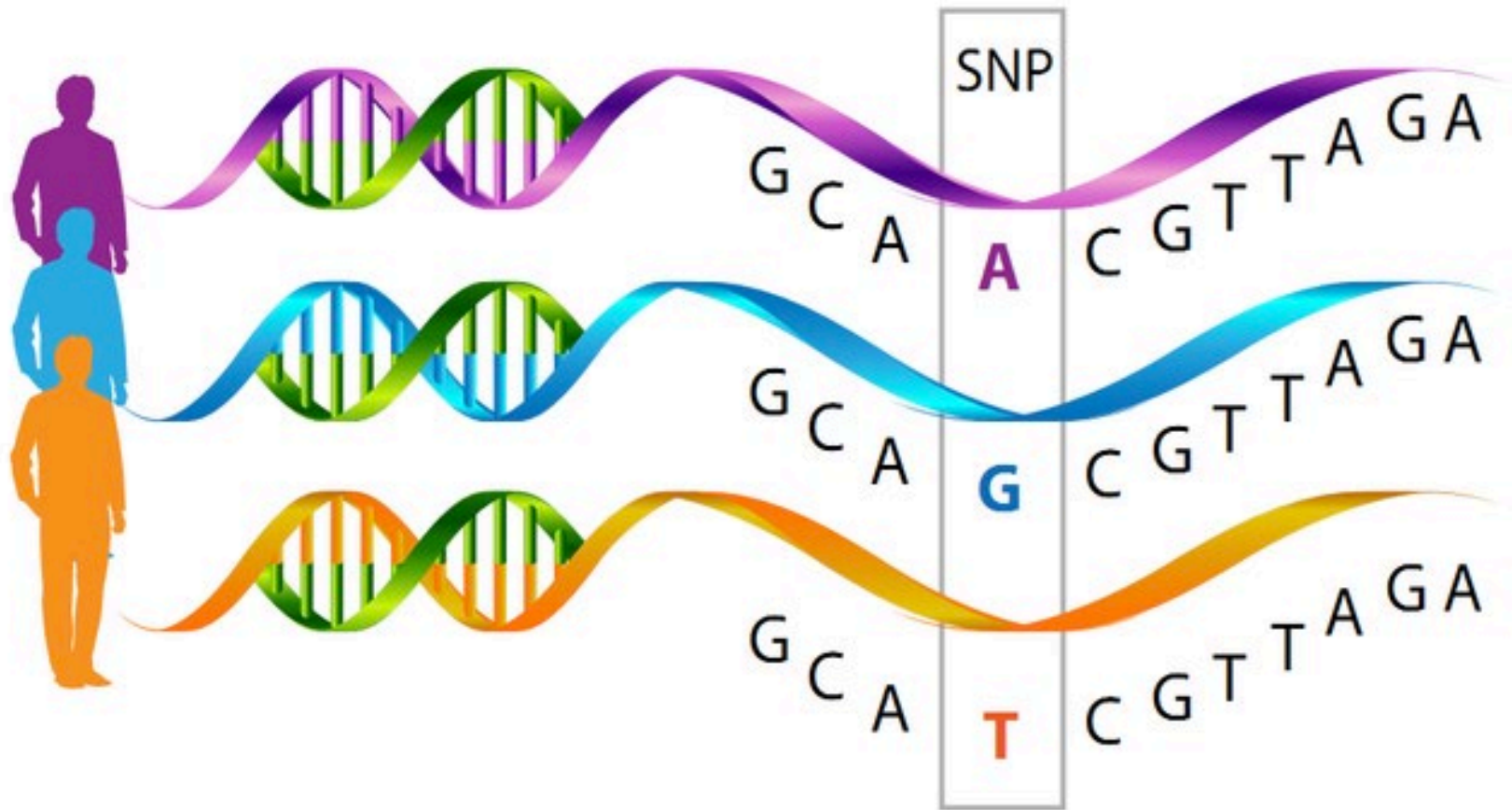
The Genomics of Neonatal Opioid Withdrawal Syndrome

- 50% of one's risk for opioid addiction is due to a combination of genetic factors
- Single nucleotide polymorphisms (SNPs) in certain genes have been identified as important influences on addiction risk, and as moderators of response to opioid therapy
- Prepronociceptin(PNOC): acts as a transmitter in the brain by modulating nociceptive behavior. Variants in the PNOC gene have been linked with risk for alcohol and drug abuse in adults.

- Levrant O, The genetics of the opioid system and specific drug addictions. Human Genetics 2012

Single Nucleotide Polymorphisms

When you examine a particular region of a chromosome from different individuals and compare them, changes in a single DNA base are found. These are called polymorphisms. Since the change is found at a single location, it is called a "single nucleotide polymorphism" or SNP.



Dopamine and Addiction

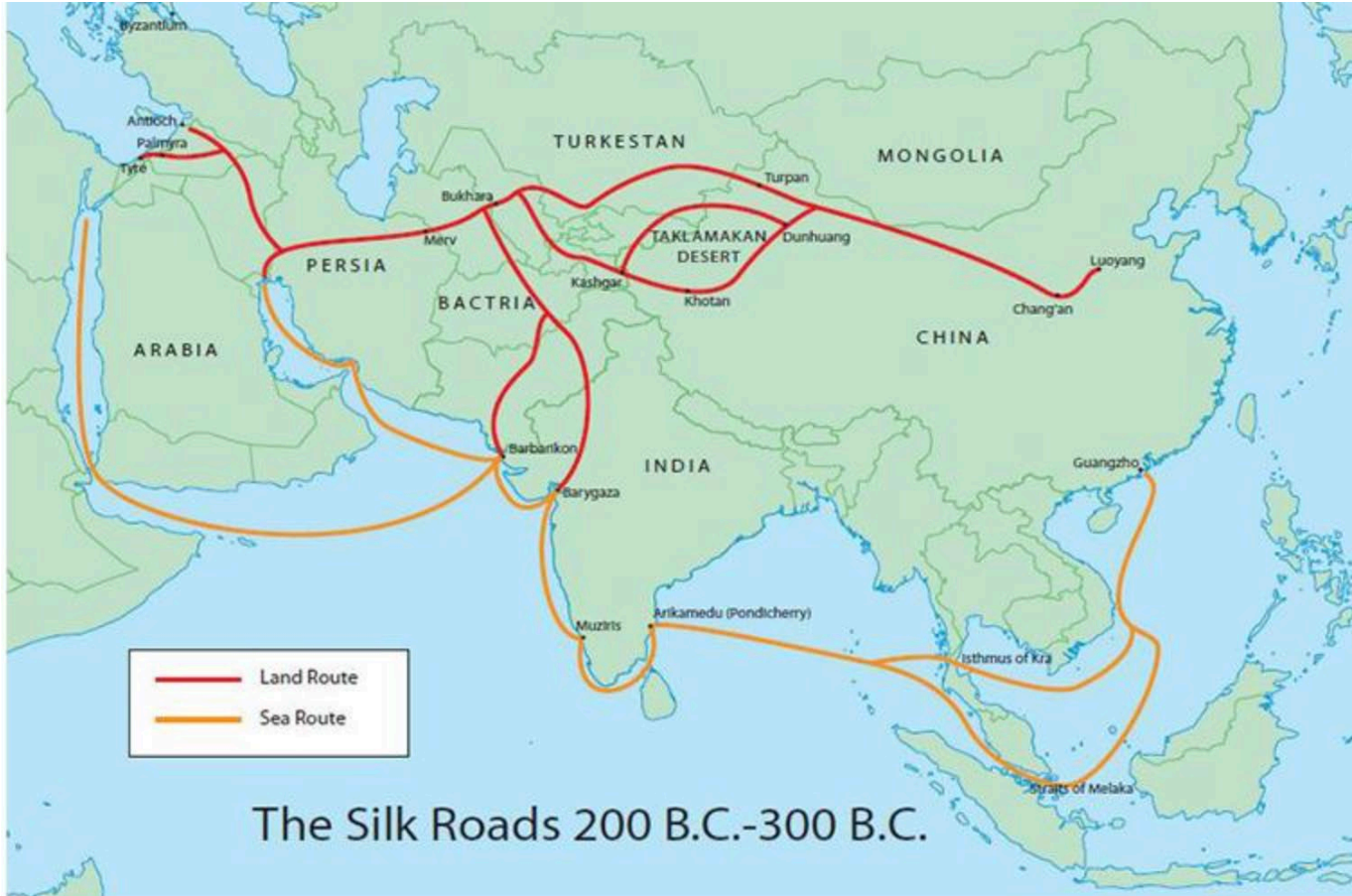
- Dopamine: the primary neurotransmitter involved in addiction. Opioids elevate the dopamine levels above baseline
- Genes whose products are involved in the dopamine pathway are crucial
- Catechol-O-methyltransferase (COMT) is the key enzyme that metabolizes dopamine in the CNS
- SNPs like **rs4680** in COMT result in a 3-4x reduction in this enzyme and therefore higher circulating dopamine levels
- Adult cancer patients with the **rs4680** minor G allele have been shown to require less morphine for pain

Opium History

- 3400 B.C. in lower Mesopotamia, Sumerians cultivated and used opium for its powers.
- Passed it on to the Assyrians, then to the Egyptians
- Over the centuries its reputation spread, and the trade stretched to India and China via the Silk Roads
- British Empire secretly smuggled it to China- fueling the Opium Wars of the 1800's
- Chinese immigrants brought opium to the US in the mid 1800's with the railroad and the Gold Rush.



The Silk Roads



Opium Den in San Francisco



Heroin History

- London, 1874: C.R. Alder Wright synthesized first heroin from opium by adding 2 acetyl groups to the molecule (diacetyl morphine).
- Germany, 1897: Felix Hoffman was working for the pharmaceutical lab now known as Bayer Labs in Elberfeld, Germany
- Hoffman re-synthesized heroin (diacetyl morphine) in an attempt to make codeine, a less potent form of morphine.
- Bayer named this new compound Heroin, from the Greek heros, or hero.



Bayer Heroin

- Marketed from 1898 to 1910 in the US as a non-addicting morphine substitute and cough suppressant
- Later became an embarrassment for Bayer when it was discovered that heroin quickly was metabolized to morphine.
- A federal law banned OTC sale in 1914
- Heroin was banned completely in 1924 by the US Congress



Heroin Production and Supply

Opium Poppy with Latex “Milk of the Poppy”



- Afghanistan: produces $\frac{3}{4}$ of the world's supply. Supplied as brown powder
- Their production in 2017 hit a record high (it increased by 63%)
- White powder heroin comes from Southeast Asia

Brookings Institute

Vanda Felbab-Brown

Senior Fellow - [Foreign Policy, Center for 21st Century Security and Intelligence](#)

November 21, 2017

There is simply nothing in Afghanistan that produces more jobs than the opium poppy economy.

Heroin in the United States

Mexican Opium Poppy



- Mexico supplies 90 % of heroin seized by the DEA
- Known by its color: “black tar” heroin
- Columbia and Guatemala supply small amounts of heroin: brown powder

It's not Just the Heroin

- Dealers are increasingly cutting the heroin with fentanyl to make it more powerful and addicting
- Most of U.S. fentanyl comes from China. It is often sent through the mail or hidden in shipments from China that go to U.S. ports of entry.
- Fentanyl is appearing more often in our umbilical cord screening

Maternal Screening and Subsequent Action

- Mother: Ideally, urine toxicology during pregnancy. This should include urine for opioids
- Mothers with positive screens are counseled, and appropriate referrals are made, e.g. to a drug rehab facility, and also to neonatologists to discuss baby's chances of withdrawal and treatment options
- Treatment with buprenorphine (Subutex) is preferable to methadone, but not always possible

Infant Screening

- Urine for toxicology
- Urine for opiates (above screen does not test for oxycodone, buprenorphine, etc.)
- Meconium toxicology- must collect all the meconium, not just one sample; reflects any exposure after 20 weeks gestation
- Infants with known exposure should remain in hospital for 5 days to assess for neonatal opioid withdrawal

Cord Tissue Testing



- A drug test that utilizes umbilical cord tissue as the sample matrix
- Universal
- Noninvasive, simple to collect
- Allows for a higher level of sensitivity for specific drugs
- Faster turnaround time than meconium screen

• USDTL.com

CordStat®

- Amphetamines
- Barbiturates
- Buprenorphine
- Benzodiazepines
- Cannabinoids
- Cocaine
- Methadone
- Meperidine
- Opioids: heroin, morphine, codeine, hydromorphone, hydrocodone
- Oxycodone
- PCP(Phencyclidine), “angel dust”
- Tramadol: non-opioid derived synthetic opioid

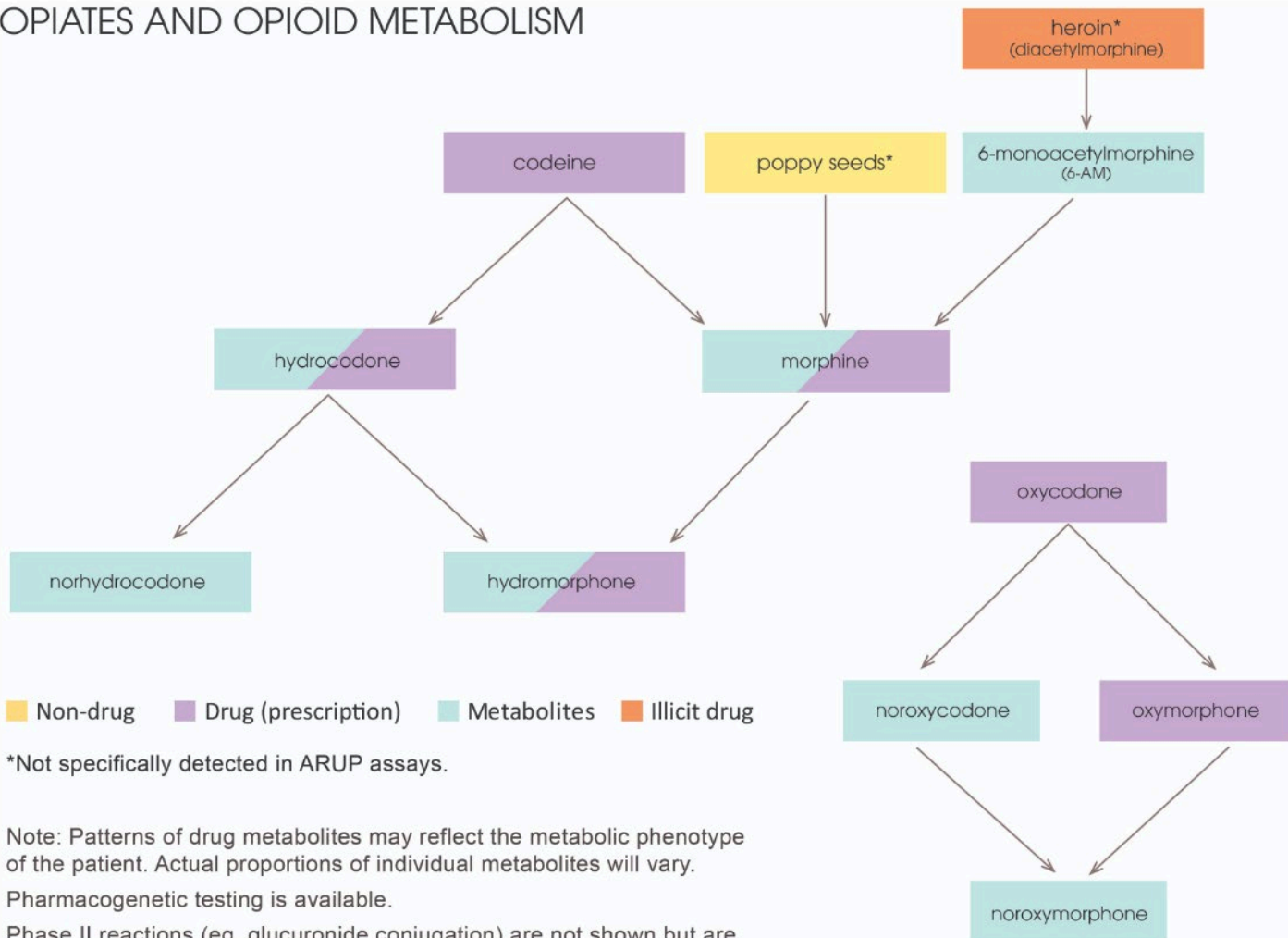


CordStat®

What does the opioid screen really tell you?

- Codeine
- Morphine
- Hydrocodone
- Hydromorphone (Dilaudid)
- 6-MAM

OPIATES AND OPIOID METABOLISM



■ Non-drug ■ Drug (prescription) ■ Metabolites ■ Illicit drug

*Not specifically detected in ARUP assays.

Note: Patterns of drug metabolites may reflect the metabolic phenotype of the patient. Actual proportions of individual metabolites will vary.

Pharmacogenetic testing is available.

Phase II reactions (eg, glucuronide conjugation) are not shown but are prominent for most compounds.

Changing Course



Old School: The Finnegan Score for Neonatal Abstinence

Tool developed by Loretta Finnegan, M.D. in 1975

Provides a quantitative measure of the severity of withdrawal symptoms

The most widely used form consists of 21 signs and symptoms grouped by system

The scoring method allows for standardization of assessment, and consistency of management of infants with NAS

Finnegan Scoring

- Nurses begin the scoring at birth, or whenever symptoms develop
- Scores are obtained every 2-4 hours, and reflect the entire time period since the previous score
- A score above 8 denotes neonatal abstinence syndrome requiring non-pharmacologic treatment and possibly treatment with opioids, phenobarbital, or both.
- Once baby is stable on treatment protocol, the scores are used for weaning

Finnegan Shortfalls

- Test was a part of a research project
- Never independently verified or replicated
- Allows for significant subjectivity
- Requires initial and repetitive training for caregivers
- Suffers from lack of inter-rater reliability
- Associated with parental anxiety

New School: The Yale Initiative to Improve Care of NAS Infants (Eat, Sleep, Console)

- Studied 287 infants from 2008 to 2016
- Interventions: Standardized care of NAS infants
 - Transfer from well nursery to inpatient unit
 - Developed novel approach to assessment
 - Rapid morphine weans
 - Prenatal counseling of parents
 - Morphine given as needed
 - Empowering messaging to parents

- Grossman M, An Initiative to Improve the Quality of Care of Infants With Neonatal Abstinence Syndrome. *Pediatrics* May 2017

Yale Initiative Outcomes

- Opioid-exposed infants who required morphine decreased from 98% to 14 %
- Costs decreased from \$44,824 to \$10,289 per hospital stay
- No infants were re-admitted for NAS, and no adverse events occurred

A Kinder, Gentler Approach: The Comfort Assessment

- We ask each day on rounds, and before each feeding:
 - 1. Can infant eat (breastfeed or take ½-1 ounce)?
 - 2. Can infant sleep at least one hour?
 - 3. Can infant be consoled within ten minutes?



Our Current Approach to NOWS

- Follow the comfort assessment
- If therapy is needed, begin with buprenorphine
- Dose: 16 mcg/kg/day (increase up to 75 mcg/kg/day)
- Phenobarbital may be added if needed
- Begin buprenorphine wean after 24-48 hours of stable comfort assessments
- Wean buprenorphine per weaning schedule

Promising New Therapies



PRN or as needed medication

- Several recent papers describe their success with treating prn rather than scheduled meds
- Currently there is a large NIH study with 27 centers: comparing prn versus scheduled morphine or buprenorphine
- Akron NICU uses morphine prn. We have used buprenorphine for the past 5 years.
- Mahoning Valley will soon begin a trial of prn morphine



Snoo Robotic Baby Bassinet



A Novel syndrome associated with prenatal fentanyl exposure

- 10 infants with physical characteristics of Smith-Lemli-Opitz syndrome
 - Findings: microcephaly, thin upper lip, short nasal tip, feeding difficulties, single palmar crease, adducted thumb 2,3 toe syndactyly, cleft palate, talipes or rocker bottom feet
 - All infants had prenatal fentanyl exposure and symptoms of NOWS
- E. Wadman, Genetics in Medicine Open, Sept 2023

New Syndrome, cont.

Smith Lemli Opitz Syndrome

- Defects in cholesterol metabolism caused by enzyme variants that are genetically transmitted
- Prenatal fentanyl exposure may inhibit the same enzymes involved in cholesterol metabolism.

This results in the physical characteristics of SLO.

The abnormalities in cholesterol metabolism subsequently resolve, but the syndrome persists (similar to fetal alcohol syndrome)

A novel syndrome



NOWS In Summary

- Neonatal Opioid Withdrawal Syndrome remains a significant problem around the world.
- Our unit has seen a steady number of affected newborns with a slight decrease in the past two years
- Maternal substance patterns change with the availability of drugs on the market or on the street
- New and promising treatments for both mother and infant are within reach.
- Our goal: minimize maternal addiction when possible



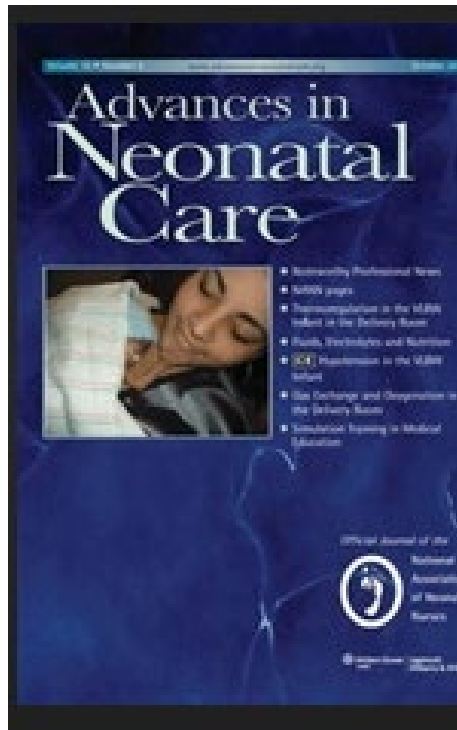
NOWS in Summary, cont.

The goal for our babies :

- Shorten their length of stay
- Maintain them in a comfortable, relatively symptom- free environment while under treatment
- Encourage maternal-infant bonding and breastfeeding when possible and appropriate
- Continue our search for novel ways to treat babies with NOWS (minimize their time on opioids)

“You’re out of the Woods”





[Eat, Sleep, Console and Adjunctive Buprenorphine Improved Outcomes in Neonatal Opioid Withdrawal Syndrome](#)

Sarrah Hein, PharmD, BCPPS; Barbara Clouser, MD; Mohammed Tamim, M. MD; Diane Lockett, MSN; Kathleen Brauer, MSN; Linda Cooper, MD
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Questions?

