Neonatal Abstinence Syndrome: What You Need to Know

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February 9, 2018

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The Child First and Always®

University of Utah School of Medicine
Department of Pediatrics

DISCLOSURES

The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.

I will discusses off-label use of medications.

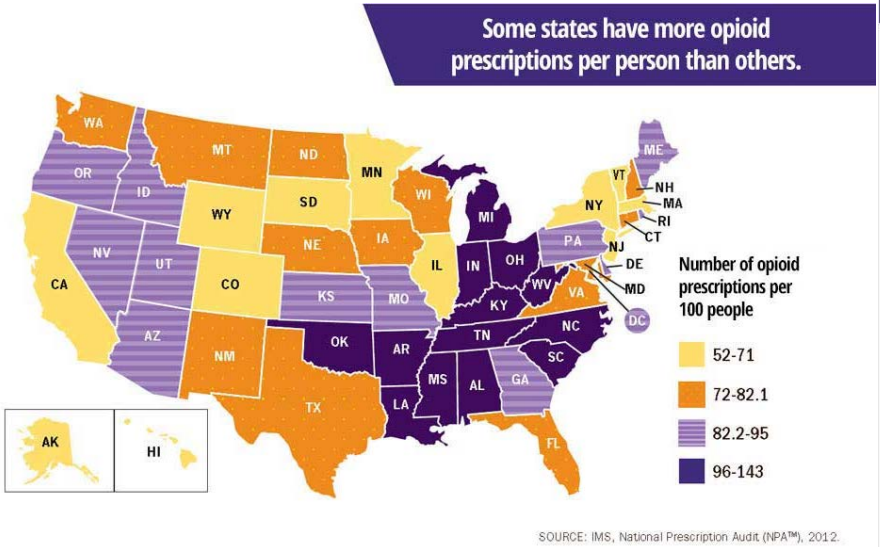
After participating in the presentation, you should have increased knowledge and enhanced competence to…

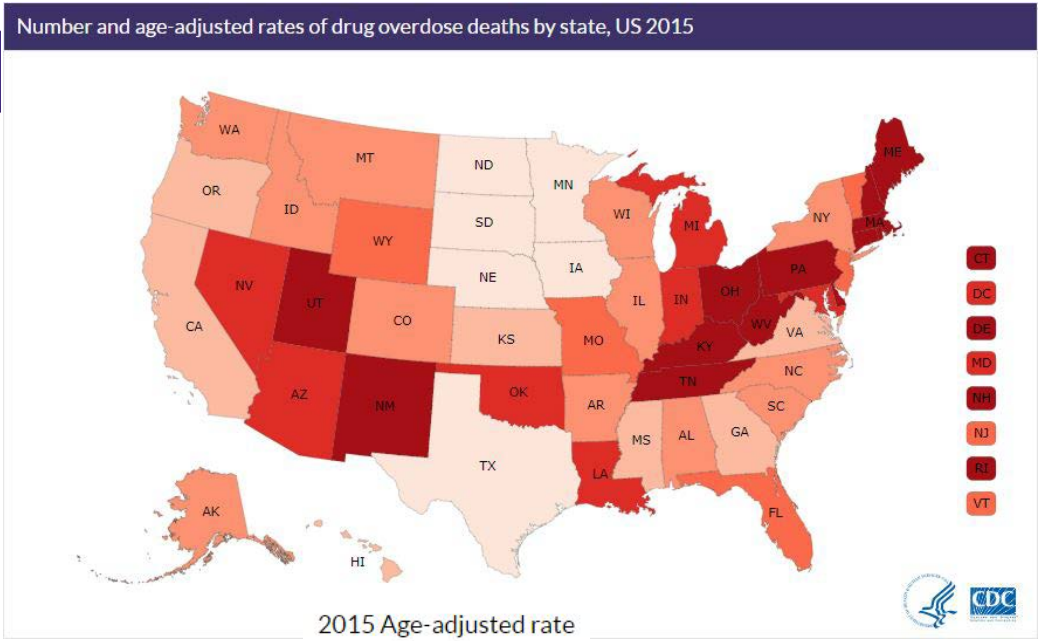
1. Define the prevalence of neonatal abstinence syndrome (NAS) nationally and locally
2. Define the clinical features of NAS
3. Illustrate management protocols that are in use to manage NAS

Opioid Pain Relievers (OPRs)

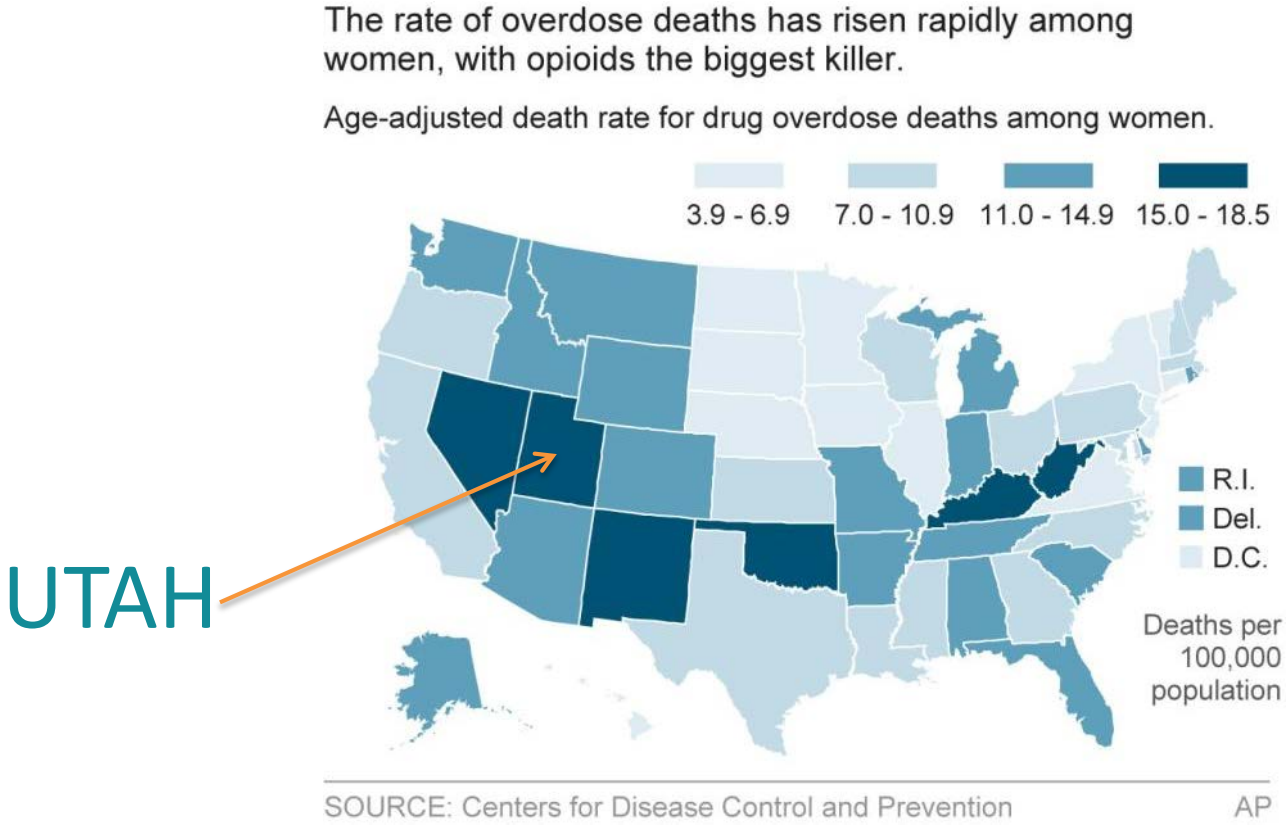
- **Prescription opioid use is widespread in the U.S.**
- **Now account for more overdose deaths than cocaine and heroin combined; More deaths than car accidents**
- **In 2010, enough OPRs were prescribed “to medicate every American adult with a standard pain treatment dose of 5mg of hydrocodone taken every 4 hours for a month”**
- **Most commonly prescribed short-acting opioids: codeine, hydrocodone, and oxycodone (1/10, 1, 1.5-2x potent than morphine respectively); long-acting opioids are methadone and buprenorphine to stabilize maternal opiate/opioid withdrawal symptoms**
- **Beware of opioid diversion! This has led to increased use of heroin as people are unable to obtain prescribed opiates/opioids.**

Public Health Problem: Opioid Prescription and Deaths in U.S.





Ignored Public Health Problem: Drug Overdose Death Rates Among Women



UTAH

Another Ignored Public Health Problem: Neonatal Abstinence Syndrome (NAS)

- The term NAS has been principally used to describe neonatal withdrawal signs/symptoms occurring after *in utero* exposure to <u>opioids</u>
  - Versus neonatal discontinuation syndrome (other prescribed medications like SSRIs, SSNRIs, benzodiapines, etc.)

Clinical features of NAS

- **Neurologic excitability**
  - Hyperactive primitive reflexes
  - Irritability/high pitched cry
  - Sleep/wake disturbance
  - Hypertonia
  - Tremors
  - Seizures
- **Gastrointestinal dysfunction**
  - Feeding difficulties
  - Uncoordinated sucking and swallowing
  - Vomiting/diarrhea
- **Autonomic signs**
  - Fever
  - Sweating
  - Nasal stuffiness/Sneezing
  - Mottling
  - Yawning

At increased risk for failure to thrive!

Clinical features of NAS

- **Vary due to:**
  - **Maternal drug history (both illicit, licit, and prescribed)**
  - **Maternal drug metabolism**
  - **Net transfer of drug across placenta**
  - **Placental metabolism**
  - **Fetal metabolism**

  - **Difficult to predict which baby will withdraw, for how long, and how severe, and when especially in light of poly-substance abuse!**

Onset of NAS symptoms

- **Majority start showing signs within 72 hours**
  - **Range is from minutes to hours after birth to up to 2 weeks**
  - **Reports of late presentation of withdrawal symptoms not described in detail in literature**
- **NAS occurs in 55-94% of opioid exposed newborns**
- **Heroin and short-acting opioids**
  - **Usually by 24 hours, seldom beyond 48 hours**
- **Methadone/Buprenorphine**
  - **24-72 hours, may be delayed until 5-7 days**

Hudak M. et al. AAP Clinical Report: Neonatal Drug Withdrawal. Pediatrics 2012;129:e540-e560, Addiction 2003;98**:**785

Neonatal Abstinence Syndrome and Associated Health Care Expenditures

United States, 2000-2009

Patrick et al. JAMA 2012;307(18):1934-40

- **Goal: provide national estimates**
  - **NAS and its complications**
  - **Maternal opiate use at time of birth**
  - **Healthcare utilization patterns of NAS**
- **Data sources:**
  - **Hospital billing data (2000-2009)**
  - **Agency for Healthcare Research and Quality**
    - **Kids' Inpatient Database (KID) for newborns**
    - **Nationwide Inpatient Sample (NIS) for mothers**

Neonatal Abstinence Syndrome and Associated Health Care Expenditures

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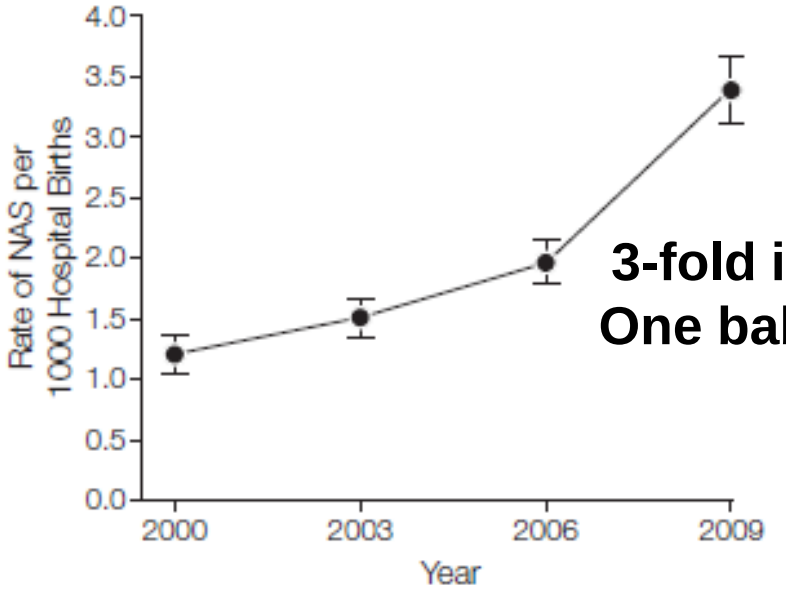
Figure 1. Weighted National Estimates of the Rates of NAS per 1000 Hospital Births per Year



3-fold increase in NAS during study period

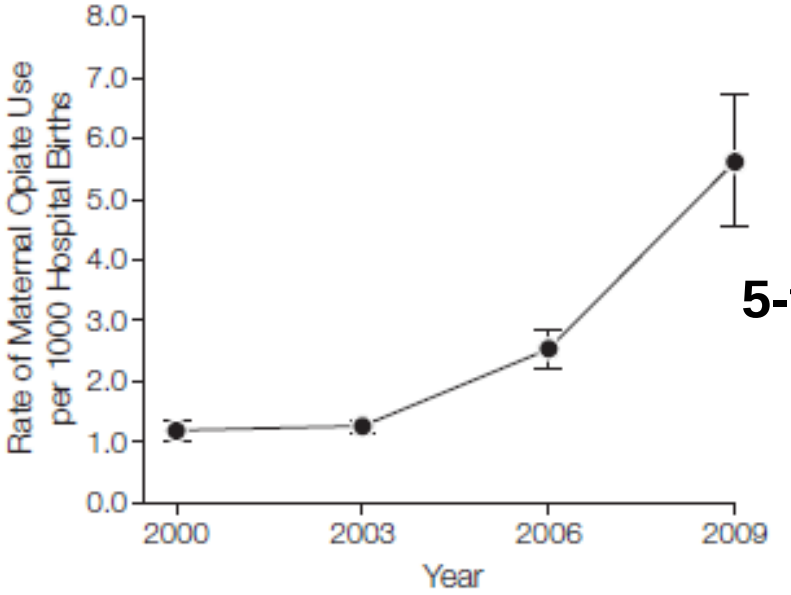
One baby born per hour in the U.S. suffers NAS

Neonatal Abstinence Syndrome and Associated Health Care Expenditures

United States, 2000-2009

Patrick et al. JAMA 2012;307(18):1934-40

Figure 2. Weighted National Estimates of the Rates of Maternal Opiate Use per 1000 Hospital Births per Year



5-fold increase in maternal opiate use

Neonatal Abstinence Syndrome and Associated Health Care Expenditures

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Patrick et al. JAMA 2012;307(18):1934-40

Table 3. Mean Hospital Charges and Length of Stay for Neonatal Abstinence Syndrome vs All Other US Births

	Mean (95% CI)				*P* for Trend
	2000	2003	2006	2009	
Neonatal Abstinence Syndrome					
Unweighted sample, No.	2920	3761	5200	9674	
Length of stay, d	15.8 (14.2-17.3)	15.9 (14.5-17.3)	15.3 (14.6-16.0)	16.4 (15.8-17.1)	.06
Hospital charges, 2009 US $	39 400 (33 400-45 400)	47 900 (40 800-55 100)	44 600 (40 400-48 900)	53 400 (49 000-57 700)	<.001
All Other US Births					
Unweighted sample, No.	784 191	890 582	1 000 203	1 113 123	
Length of stay, d	3.1 (3.0-3.1)	3.2 (3.1-3.2)	3.2 (3.2-3.3)	3.3 (3.3-3.4)	<.001
Hospital charges, 2009 US $	6600 (5800-7300)	7300 (6900-7600)	8200 (7800-8600)	9500 (9000-9900)	<.001

Hospital charges quadrupled adjusting for inflation!

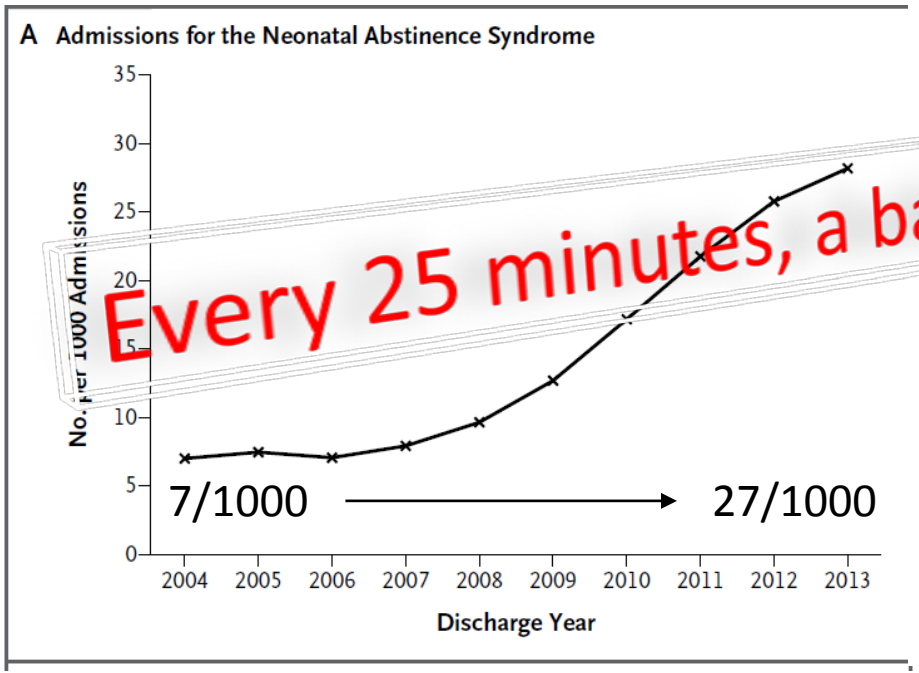
Table 4. Proportions of US Hospital Charges for Neonatal Abstinence Syndrome by Payer[a]

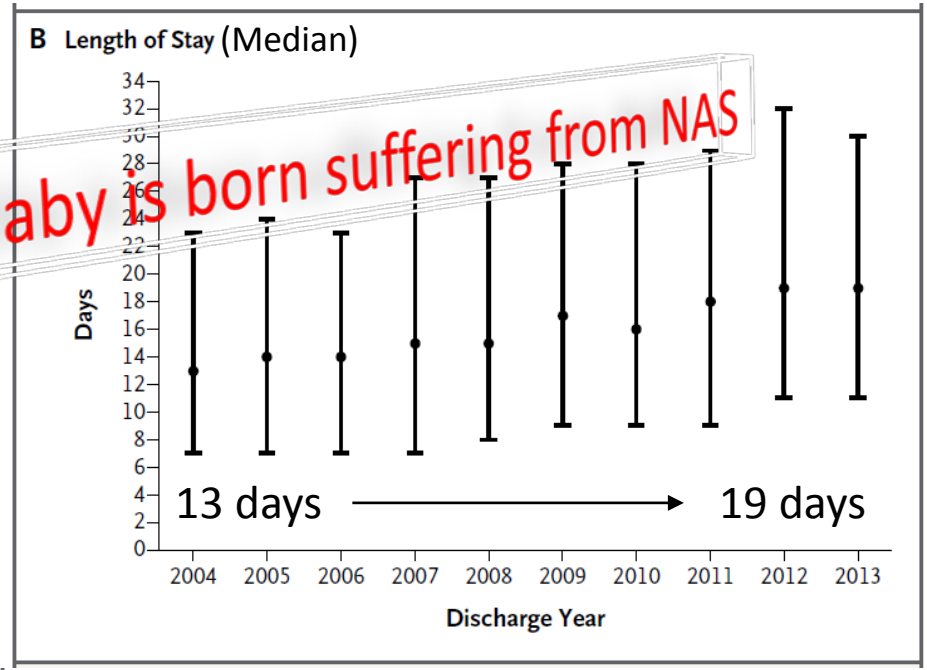
		Weighted % (95% CI)			
Year	Unweighted Sample, No.	Medicaid	Private Payer	Self-pay	Other Payer
2000	2920	68.7 (63.3-76.7)	18.2 (14.6-22.5)	8.7 (5.6-13.3)	4.4 (2.0-9.3)
2003	3761	69.9 (65.9-73.6)	19.8 (16.9-23.1)	6.5 (4.5-9.3)	3.8 (1.6-8.7)
2006	5200	73.7 (70.4-76.7)	19.0 (16.4-22.0)	5.5 (4.4-6.9)	1.9 (1.3-2.8)
2009	9674	77.6 (74.4-80.4)	17.6 (15.1-20.4)	2.9 (2.4-3.4)	2.0 (1.4-2.9)

[a] Percentages may not sum to 100 because of rounding.

Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs

Tolia et al. NEJM 2015;DOI:10.1056/NEJMsa1500439





Every 25 minutes, a baby is born suffering from NAS

Total % of NICU days nationwide attributed to NAS increased from 0.6% to 4%,
with 8 centers reporting >20% of all NICU days attributed to NAS

National Estimates of NAS

Morbidity and Mortality Weekly Report

Incidence of Neonatal Abstinence Syndrome — 28 States, 1999–2013

Jean Y. Ko, PhD[1]; Stephen W. Patrick, MD[2]; Van T. Tong, MPH[1]; Roshni Patel, MPH[1]; Jennifer N. Lind, PharmD[3]; Wanda D. Barfield, MD[1]

- Of ~30 million births that occurred from 1999-2013 in 28 states, ~75,000 NAS cases = 2.5 cases/1,000 hospital births
- 1.5 cases/1,000 births (1999, 14 states) → 6.0 cases/1,000 births (2013, 21 states) = ↑~300%
- Kentucky, Maine, Vermont, West Virginia had highest NAS incidence (Tennessee, New Hampshire not included)

National Estimates of NAS

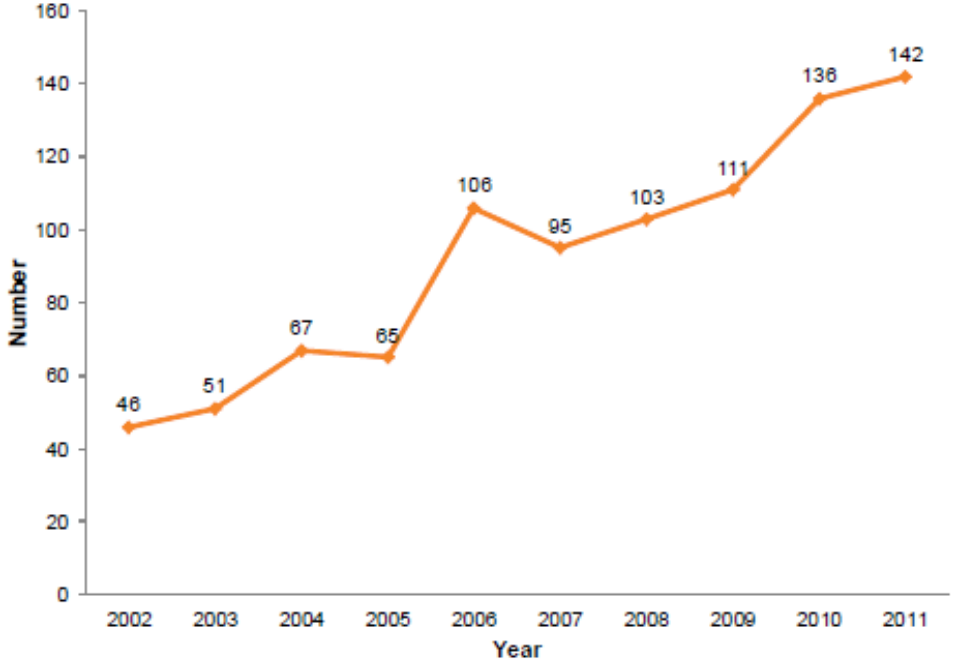
TABLE. Neonatal abstinence syndrome (NAS) incidence rates per 1,000 hospital births,* by state and year — State Inpatient Databases, Healthcare Cost and Utilization Project, 1999–2013†

State	Year															Annual change in incidence rate§
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	
Arizona	1.3	1.0	1.0	1.0	1.1	1.3	1.1	1.0	1.2	1.5	1.7	2.6	3.6	3.6	3.9	0.2
Arkansas	—¶	—¶	—¶	—¶	—¶	0.4	0.9	0.4	0.7	1.0	1.3	1.4	2.2	2.7	2.6	0.3
California	1.2	1.2	1.2	—¶	1.1	1.1	1.1	1.0	1.0	1.1	1.2	1.3	1.3	—¶	—¶	—¶
Colorado	0.4	0.6	0.6	0.7	0.6	0.9	0.9	0.9	1.3	1.3	1.4	2.3	2.5	2.8	2.9	0.2
Florida	0.4	0.4	0.5	0.6	0.7	0.7	0.9	1.3	1.7	2.3	3.4	4.9	5.9	5.9	6.3	0.6
Hawaii	—¶	0.1	0.4	0.1	0.4	0.6	—¶	0.6	0.5	0.7	0.5	0.7	0.8	0.8	0.7	0.05
Iowa	0.3	0.4	0.3	0.5	0.6	0.4	0.4	0.5	0.6	0.7	0.8	1.1	1.3	1.9	2.2	0.1
Kentucky	—¶	0.4	0.9	1.3	2.0	2.4	2.5	3.3	3.8	4.7	6.4	7.8	10.5	12.3	15.0	1.3
Maine	1.1	0.9	2.0	3.0	5.2	—¶	—¶	—¶	12.6	15.5	19.0	21.5	21.3	30.4	—¶	3.0
Maryland	7.6	6.5	7.1	6.7	6.3	6.2	6.6	6.6	6.5	7.1	8.2	9.5	10.6	11.4	—¶	0.3
Massachusetts	2.2	2.5	2.7	2.6	2.9	3.8	4.4	5.0	6.1	6.7	8.5	10.0	10.8	12.5	—¶	0.9
Michigan	—¶	0.4	0.5	0.6	0.8	0.9	1.2	1.2	1.7	2.0	2.9	3.6	5.0	5.4	6.7	0.6
Mississippi	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	1.2	1.3	—¶	—¶	—¶
Nebraska	—¶	—¶	0.2	0.1	0.3	0.2	0.7	0.4	0.2	0.4	0.7	1.0	0.8	1.4	1.6	0.1
Nevada	—¶	—¶	—¶	1.1	0.8	1.3	1.5	1.2	1.3	1.6	2.0	3.0	3.3	5.0	4.8	0.4
New Jersey	3.3	3.2	3.5	3.0	3.1	2.6	2.9	2.5	2.7	2.8	3.4	4.1	4.6	5.0	5.2	0.1
New Mexico	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	3.7	4.2	5.8	7.8	8.5	1.5
New York	1.4	1.5	1.3	1.2	1.2	1.3	1.2	1.2	1.4	1.5	1.8	1.9	2.6	2.8	3.6	0.1
North Carolina	—¶	0.3	0.4	0.7	0.7	0.9	1.3	1.3	1.6	1.7	2.7	3.5	4.2	5.3	6.4	0.6
Oregon	1.0	1.0	1.2	1.5	1.3	2.1	2.1	2.0	2.0	2.3	2.9	3.7	4.4	4.5	5.0	0.3
Rhode Island	—¶	—¶	—¶	2.8	3.3	3.5	4.6	3.4	5.1	5.6	6.0	5.8	8.1	7.3	—¶	0.5
South Carolina	1.3	0.9	0.6	0.4	0.7	1.1	1.1	1.5	1.3	1.5	1.9	2.2	2.7	3.3	3.9	0.2
South Dakota	—¶	—¶	—¶	—¶	—¶	—¶	—¶	—¶	0.2	0.9	0.8	1.0	1.3	0.8	0.8	—¶
Utah	—¶	0.8	0.9	1.3	1.0	1.3	2.0	1.9	2.3	2.5	2.5	3.5	4.1	—¶	—¶	0.3
Vermont	—¶	—¶	0.7	2.7	3.7	4.1	8.1	9.1	12.5	15.8	20.9	25.3	26.2	30.5	33.3	3.6
Washington	1.5	1.3	1.6	1.7	2.1	2.7	3.5	3.4	3.2	3.6	4.5	5.6	6.7	6.9	7.9	0.5
West Virginia	—¶	0.5	1.0	1.7	3.3	3.4	6.9	7.1	7.5	10.2	11.0	14.2	16.9	21.7	33.4	2.7
Wisconsin	0.4	0.4	0.3	0.5	0.6	1.1	0.9	1.7	1.9	2.5	2.9	4.1	5.5	5.7	7.9	0.7

NAS in Utah

Complicated Pregnancies or Births due to a Mother's Drug Dependence

Figure 1. Number of hospital discharges as a result of complicated pregnancies or births due to a mother's drug dependence, Utah, 2002–2011



Source: Utah Hospital Discharge Data

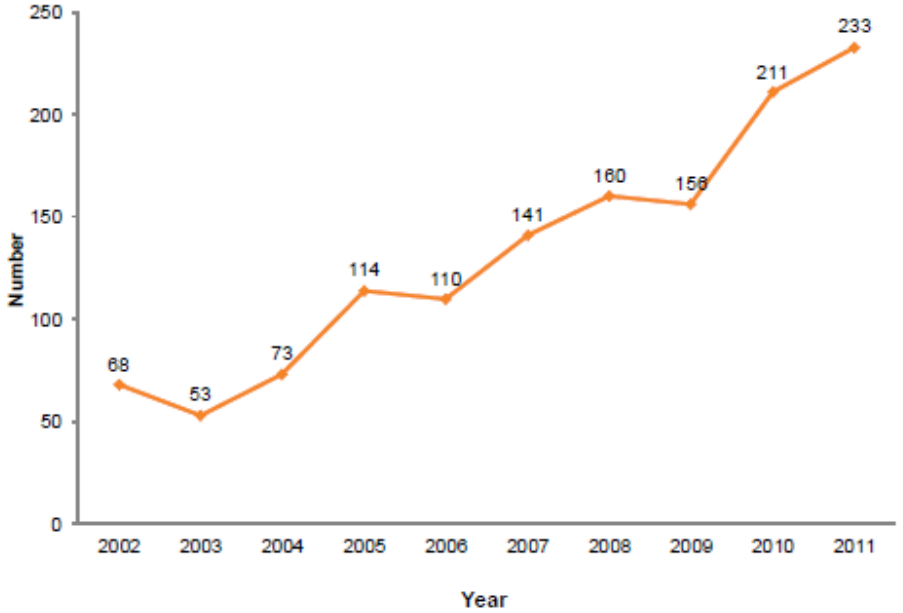
Utah Department of Health Status Update 7/2013

NAS in Utah

- Over the past decade, the number of Utah newborns diagnosed with NAS increased ~243% (not including latest numbers)

Newborns with Neonatal Abstinence Syndrome

Figure 2. Number of newborns (birth to 28 days) with NAS, Utah, 2002–2011



Source: Utah Hospital Discharge Data

Latest numbers

2012: 272

2013: 275

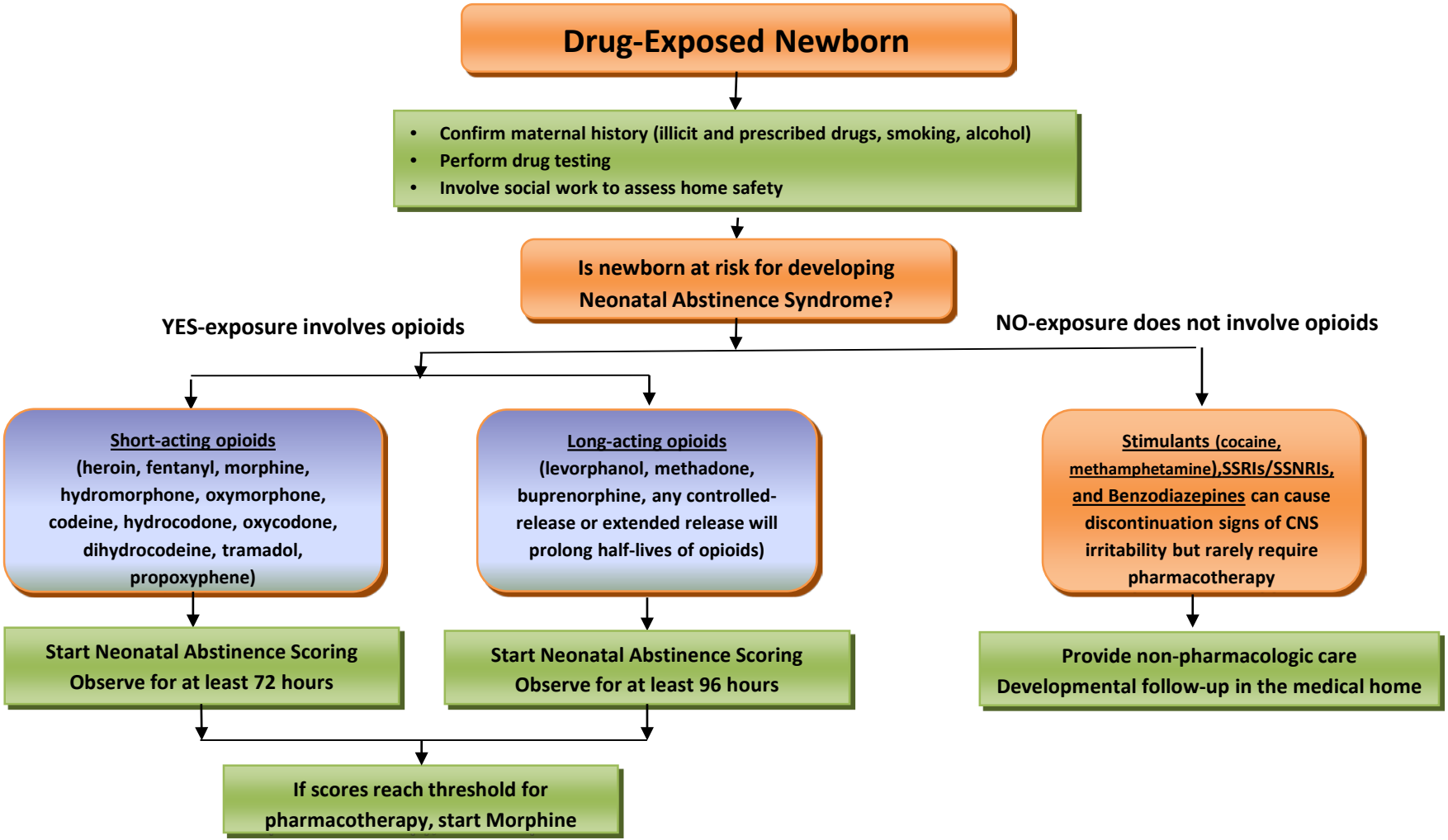
2014: 310

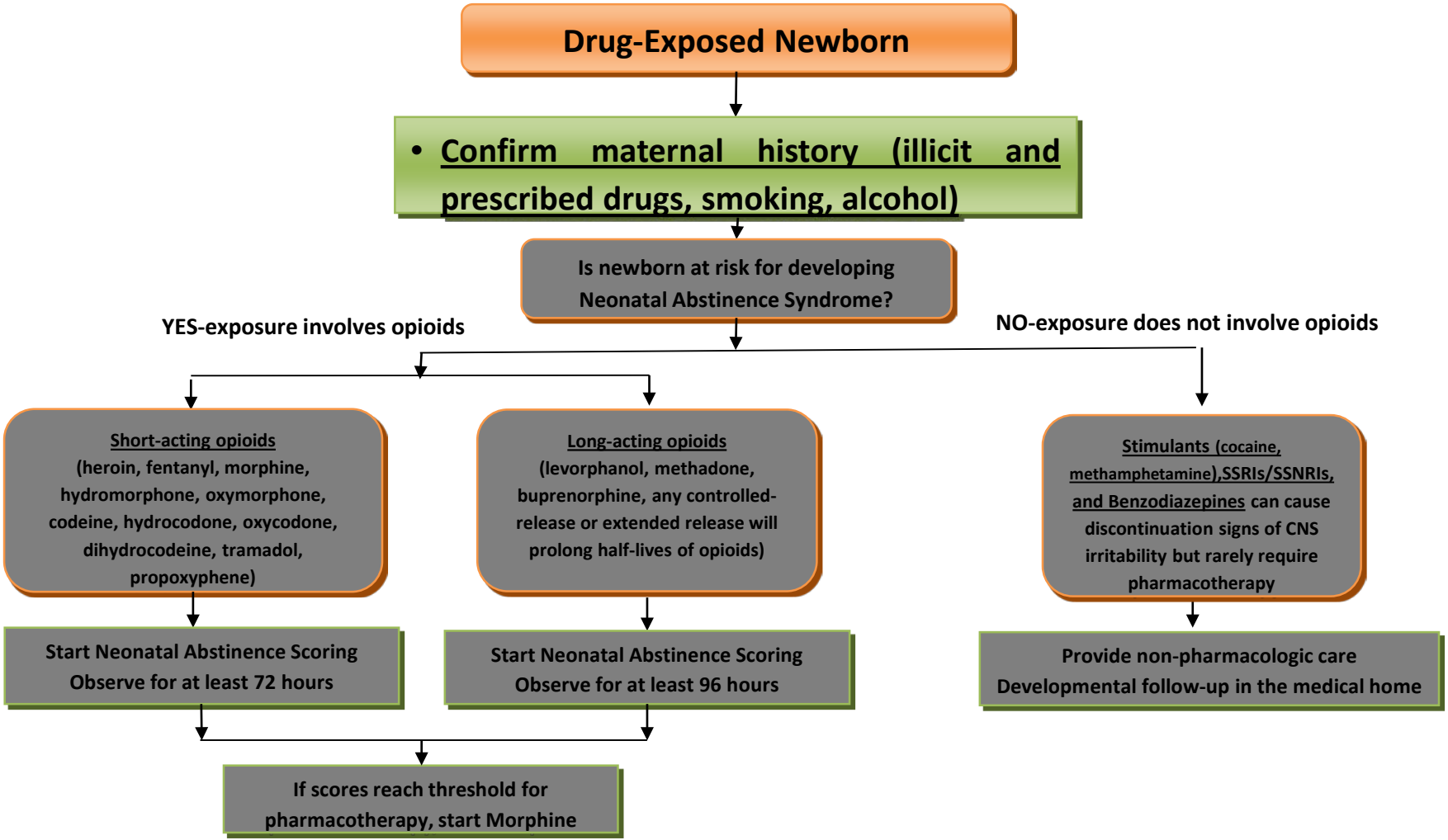
Utah Department of Health Status Update 7/2013

Skyrocketing increase in NAS

- **Every nursery should:**
- **Have a policy for assessing maternal substance abuse**
- **Have a standardized plan for the evaluation and management of infants at risk for or showing withdrawal**

Hudak M. et al. AAP Clinical Report: Neonatal Drug Withdrawal. Pediatrics.2012;129:e540-e560


Drug-Exposed Newborn
• Confirm maternal history (illicit and prescribed drugs, smoking, alcohol)
• Perform drug testing
• Involve social work to assess home safety
Is newborn at risk for developing Neonatal Abstinence Syndrome?
YES-exposure involves opioids
NO-exposure does not involve opioids
Short-acting opioids (heroin, fentanyl, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, dihydrocodeine, tramadol, propoxyphene)
Long-acting opioids (levorphanol, methadone, buprenorphine, any controlled-release or extended release will prolong half-lives of opioids)
Stimulants (cocaine, methamphetamine),SSRIs/SSNRIs, and Benzodiazepines can cause discontinuation signs of CNS irritability but rarely require pharmacotherapy
Start Neonatal Abstinence Scoring Observe for at least 72 hours
Start Neonatal Abstinence Scoring Observe for at least 96 hours
Provide non-pharmacologic care Developmental follow-up in the medical home
If scores reach threshold for pharmacotherapy, start Morphine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Maternal History (5 “P”s)

Parents

Did your parents have problems with alcohol or other drug use?

Peers

Do any of your friends have problems with alcohol or other drug use?

Partner

Does your partner have problems with alcohol or other drug use?

Past

In the past, have you had difficulties in your life due to alcohol or other drugs, including prescription medications

Present

In the past month, have you drunk any alcohol or used other drugs?

Adapted from Chasnoff et al. The 4P’s Plus© Screen for substance use in pregnancy: Clinical Application and Outcomes. *J Perinatology* (2005) 25, 368-374.

Maternal History High Risk Characteristics

No prenatal care
Previous unexplained fetal demise
Precipitous labor
Abruptio placentae
Hypertensive episodes
Severe mood swings
Cerebrovascular accidents/stroke
Myocardial infarction
Unexplained repeated spontaneous abortions

Neonatal History
High Risk Characteristics

Unexplained seizures or apneic spells

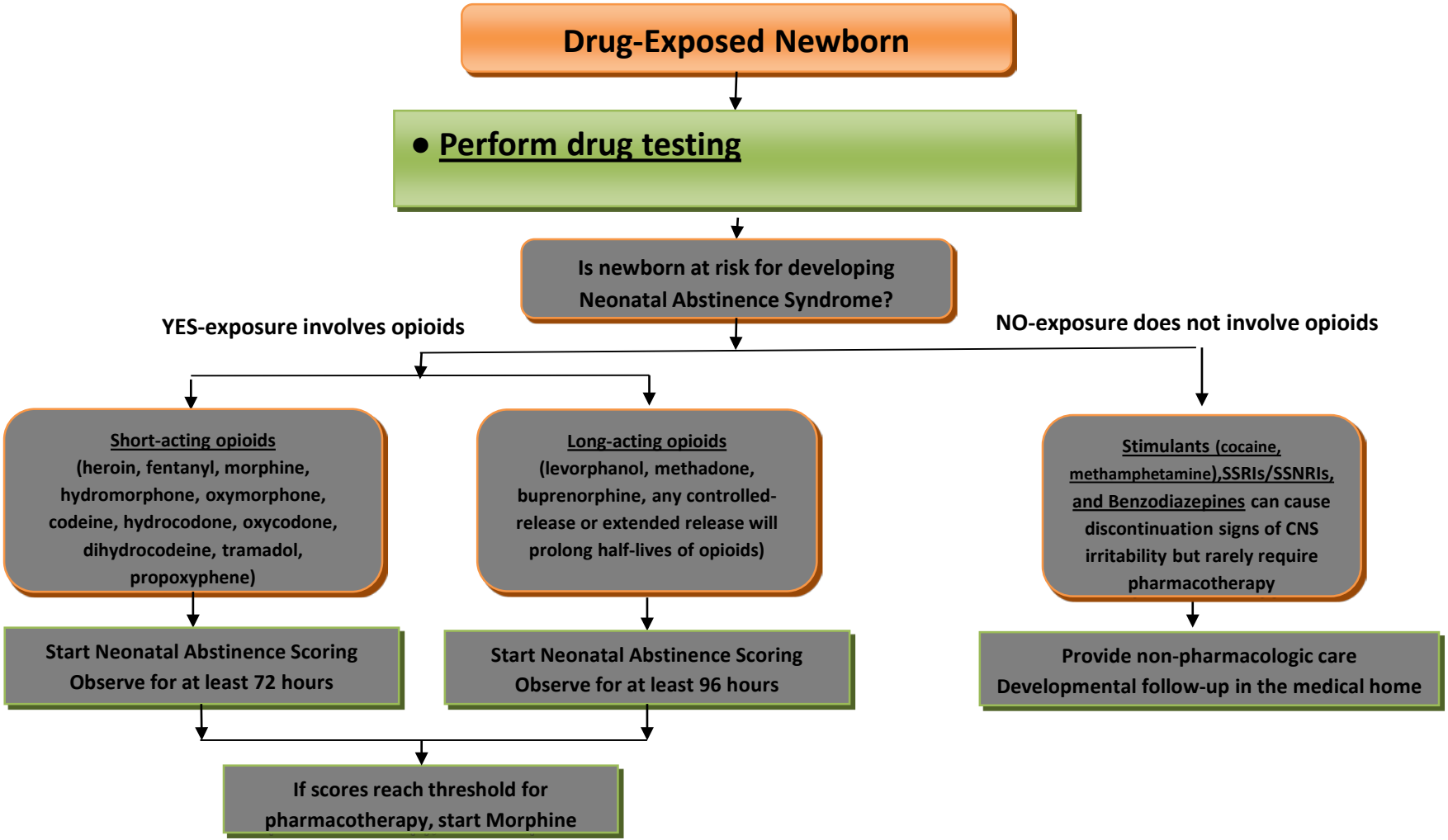
Unexplained symmetric intrauterine growth restriction

Atypical vascular incidents such as stroke

Myocardial infarction

Unexplained NEC

Signs of neonatal abstinence syndrome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Determining drug exposure

Maternal or neonatal urine

- **Only reflects ~ 72 hours of exposure**

Meconium

- **Newborn's first stool**
  - **Reflects drug-exposure from 12-18 weeks gestation onward**
  - **Collection can be challenging/missed especially with unknown exposure history**
  - **Delayed passage in preterm infants**

Umbilical cord

Reflects use from ~12 weeks gestation onward

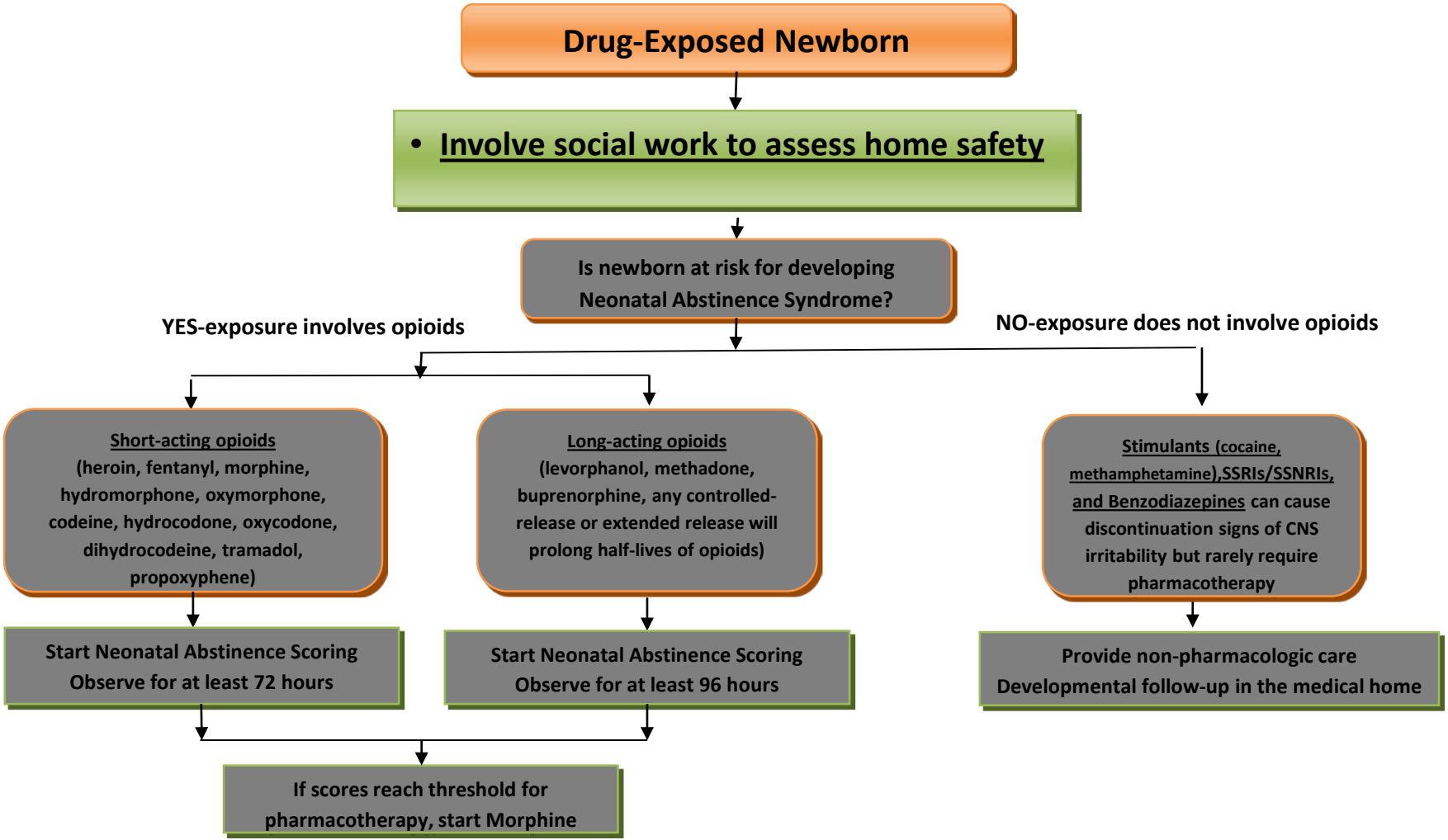
Shown to be similar to meconium in sensitivity

Easier to collect

Qualitatively detects nearly 60 drugs/drug metabolites in cord tissue (ARUP Laboratories, Salt Lake City, UT; no further confirmatory testing needed)

Turnaround time in 1-3 days

Montgomery D, et al. Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium. *Perinatol*. 2006 Jan 1;26: 11-14.United States Drug Testing Laboratories CordStat SM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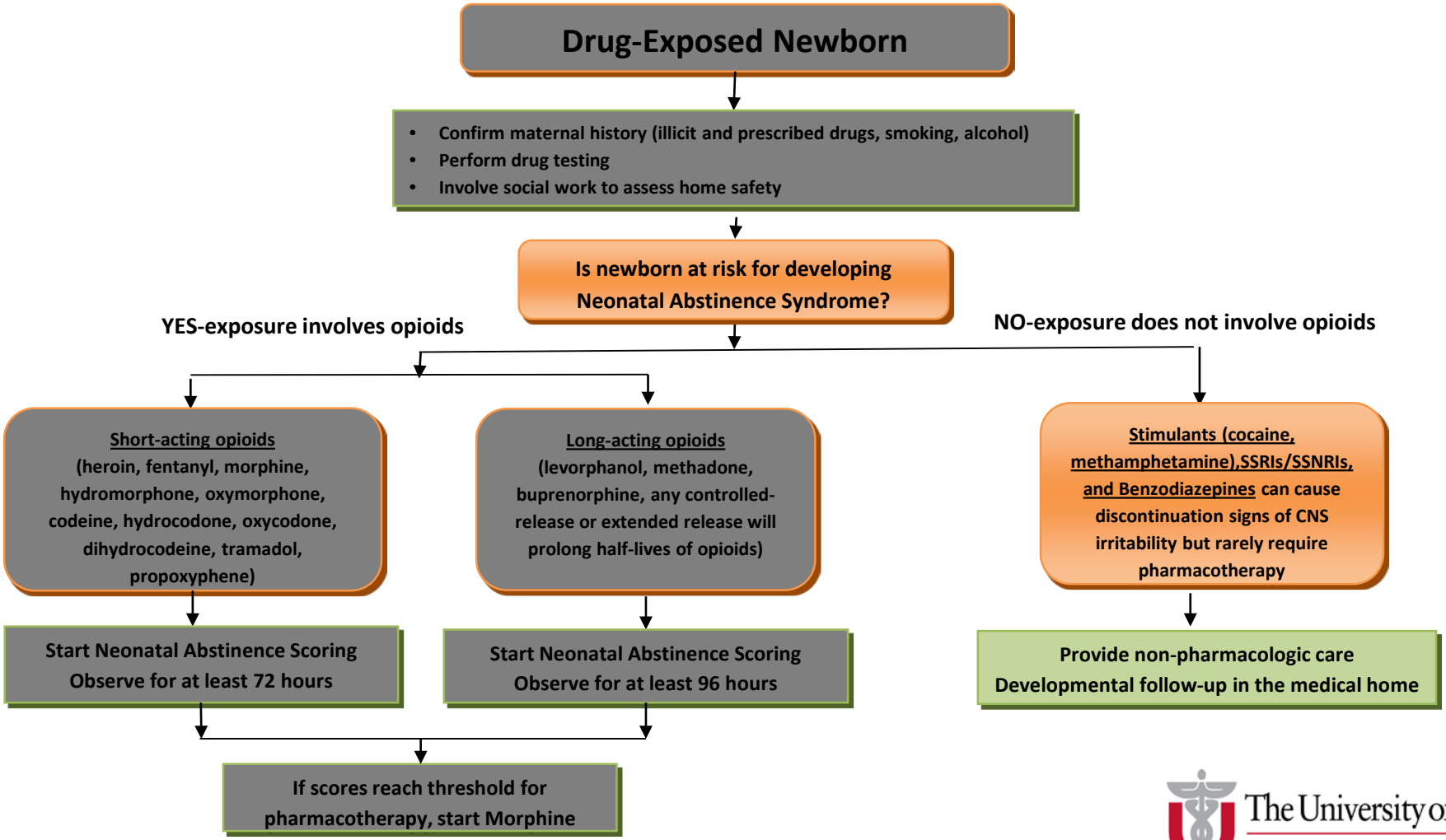

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Non-Pharmacologic Treatment

Swaddling with soft blankets

Quiet, dark environment

Frequent small feedings of hypercaloric formula (controversial)

Try a pacifier

Kangaroo care

Organize care to minimize handling

Swings – helpful for some

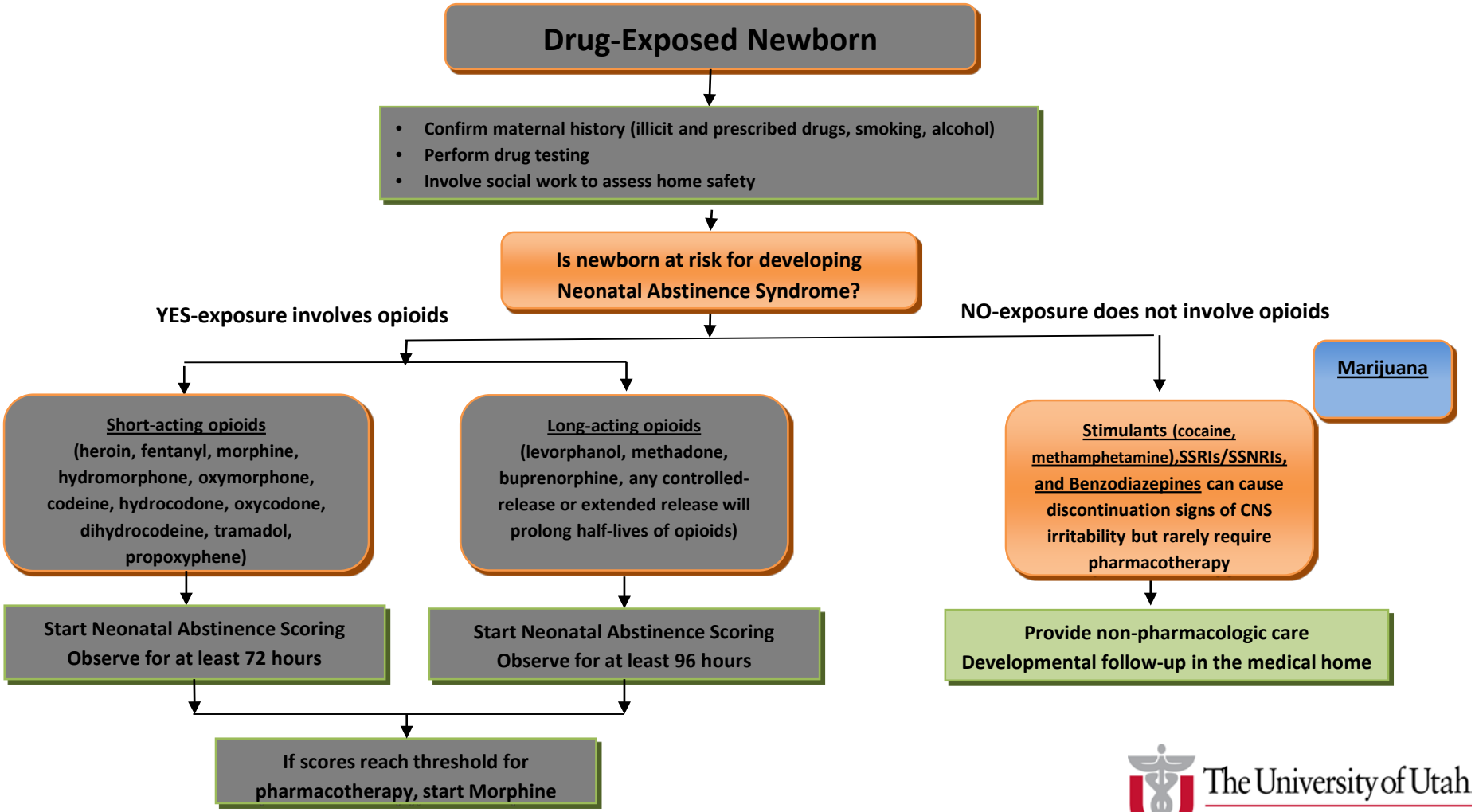
Determine level of stimulation infant can tolerate

Velez, Jansson. *J Addict Med.* 2008; 1:113-120

Non-Pharmacologic Treatment

Parent teaching

- Explain how withdrawal is affecting the infant's ability to cope with stimulation
- Explain how to decrease stimulation
- Help parents find out how much the infant will tolerate



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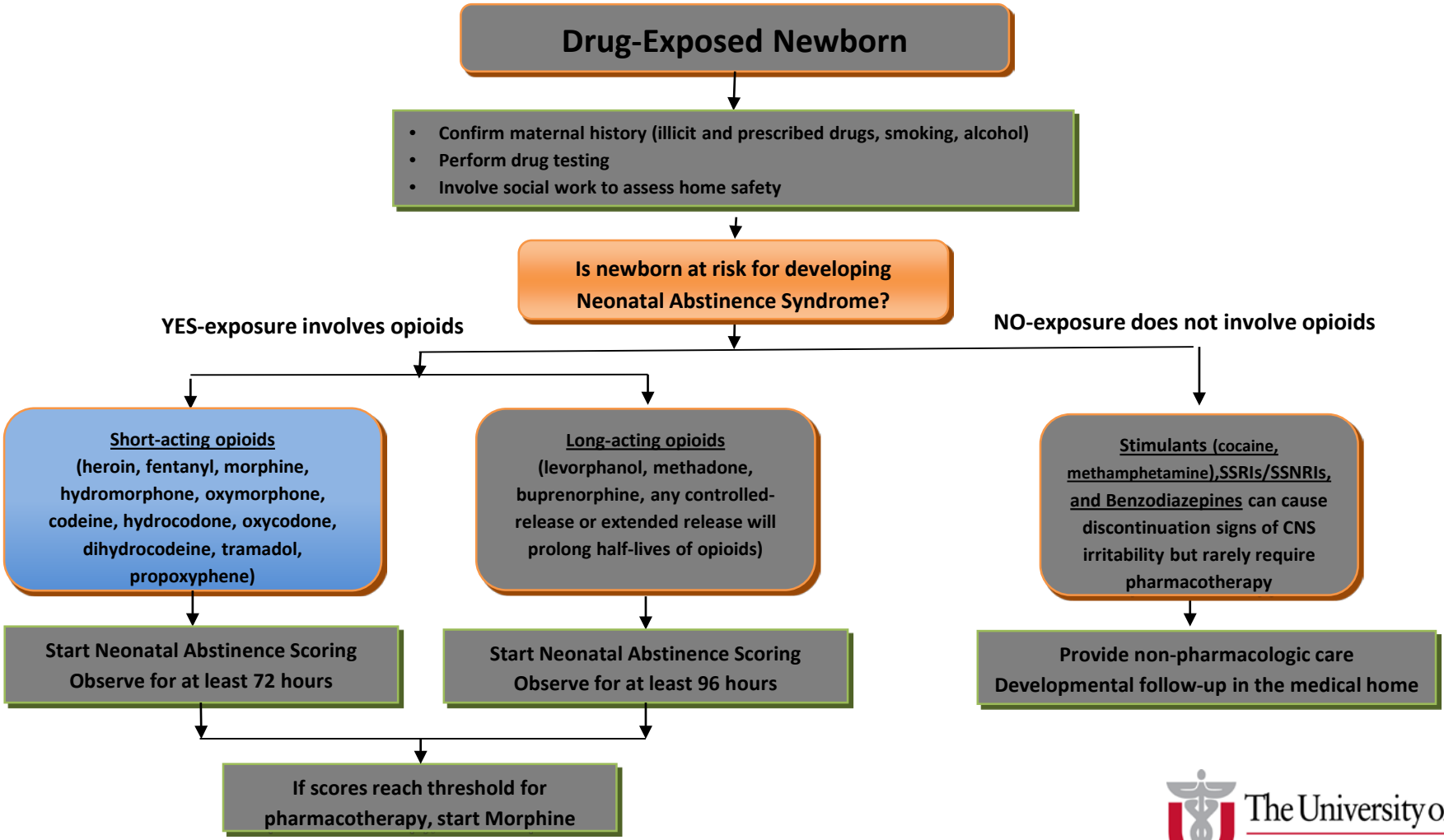

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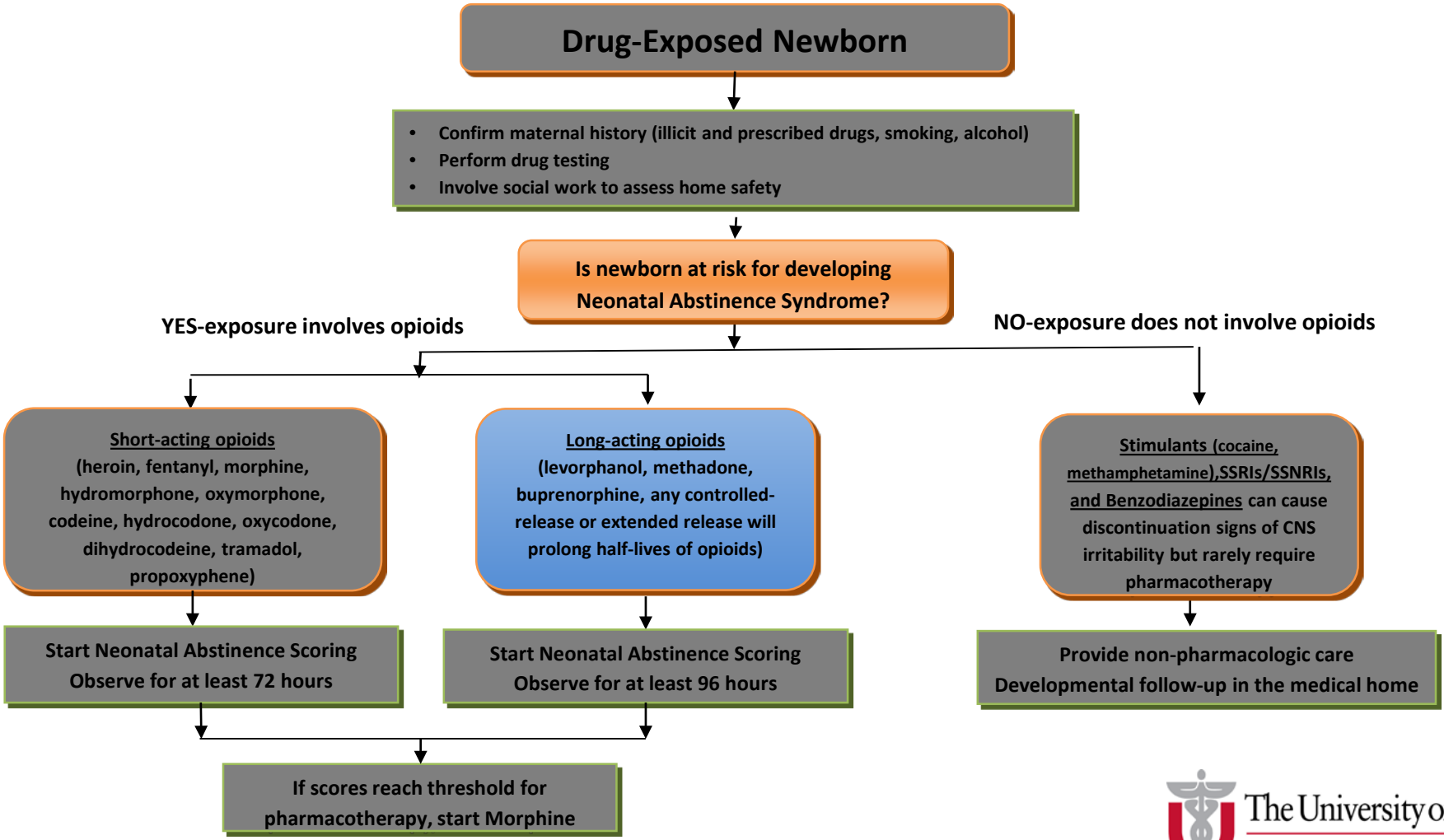

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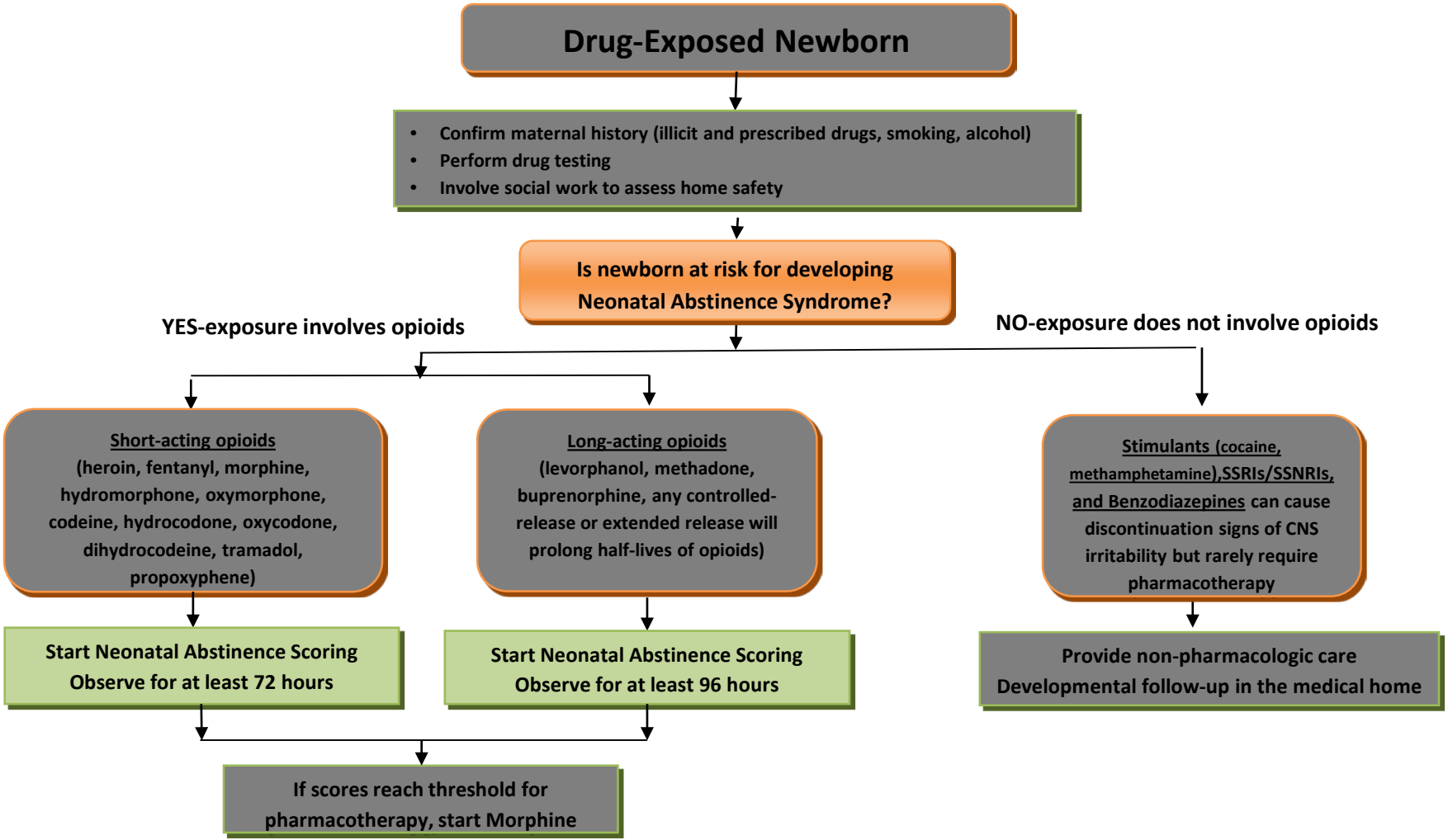

Drug-Exposed Newborn
Confirm maternal history (illicit and prescribed drugs, smoking, alcohol)
Perform drug testing
Involve social work to assess home safety
Is newborn at risk for developing Neonatal Abstinence Syndrome?
YES-exposure involves opioids
NO-exposure does not involve opioids
Short-acting opioids (heroin, fentanyl, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, dihydrocodeine, tramadol, propoxyphene)
Long-acting opioids (levorphanol, methadone, buprenorphine, any controlled-release or extended release will prolong half-lives of opioids)
Stimulants (cocaine, methamphetamine),SSRIs/SSNRIs, and Benzodiazepines can cause discontinuation signs of CNS irritability but rarely require pharmacotherapy
Start Neonatal Abstinence Scoring Observe for at least 72 hours
Start Neonatal Abstinence Scoring Observe for at least 96 hours
Provide non-pharmacologic care Developmental follow-up in the medical home
If scores reach threshold for pharmacotherapy, start Morphine

Length of observation

- **5 days of observation detected over 95% of newborns with NAS requiring pharmacotherapy**

Smirk, et al. J Paediatrics and Child Health 2014; 50: 352-355

Behavioral scoring systems

Neonatal Abstinence Scoring System

Finnegan, 1975 (gold standard)

Neonatal Drug Withdrawal Scoring System

Lipsitz, 1975

Neonatal Withdrawal Inventory

Zahorodny, 1998

FINNEGAN NEONATAL ABSTINENCE SCORE

	Signs and Symptoms	Score	AM	PM	Comments
Central Nervous System Disturbances	Excessive High Pitched Cry	2			
	Continuous High Pitched Cry	3			
	Sleeps < 1 Hour After Feeding	3			
	Sleeps < 2 Hours After Feeding	2			
	Sleeps < 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 (Specify Area:_____)	1			
	Myoclonic Jerks	3			
	Generalized Convulsions	5			
Metabolic/Vasomotor/ Respiratory Disturbances	Sweating	1			
	Fever < 38.3	1			
	Fever > 38.3	2			
	Frequent Yawning	1			
	Mottling	1			
	Nasal Stuffiness	2			
	Sneezing	1			
	Nasal Flaring	2			
	Respiratory Rate > 60/min	1			
	Respiratory Rate > 60 with retractions	2			
Gastrointestinal Disturbances	Excessive Sucking	1			
	Poor Feeding	2			
	Regurgitation	2			
	Projectile Vomiting	3			
	Loose Stools	2			
	Watery Stools	3			
	TOTAL SCORE				
	INITIALS OF SCORER				

LIPSITZ NEONATAL DRUG WITHDRAWAL SCORING SYSTEM				
	Score			
Signs	**0**	**1**	**2**	**3**
Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate or marked increased when undisturbed--subside when fed or held snugly	Marked increase or continuous even when undisturbed, going on to seizure-like movements
Irritability (excessive crying)	None	Slightly increased	Moderate to severe when disturbed or hungry	Marked even when undisturbed
Reflexes	Normal	Increased	Markedly increased	
Stools	Normal	Explosive, but normal frequency	Explosive, more than 8 per day	
Muscle tone	Normal	Increased	Rigidity	
Skin abrasions	No	Redness of knees and elbows	Skin breakdown	
Respiratory rate/min	< 55	55-75	>76	
Repetitive sneezing	No	Yes		
Repetitive yawning	No	Yes		
Vomiting	No	Yes		
Fever	No	Yes		

Neonatal Withdrawal Inventory NWI (adopted by IHC and UUHC, Utah)

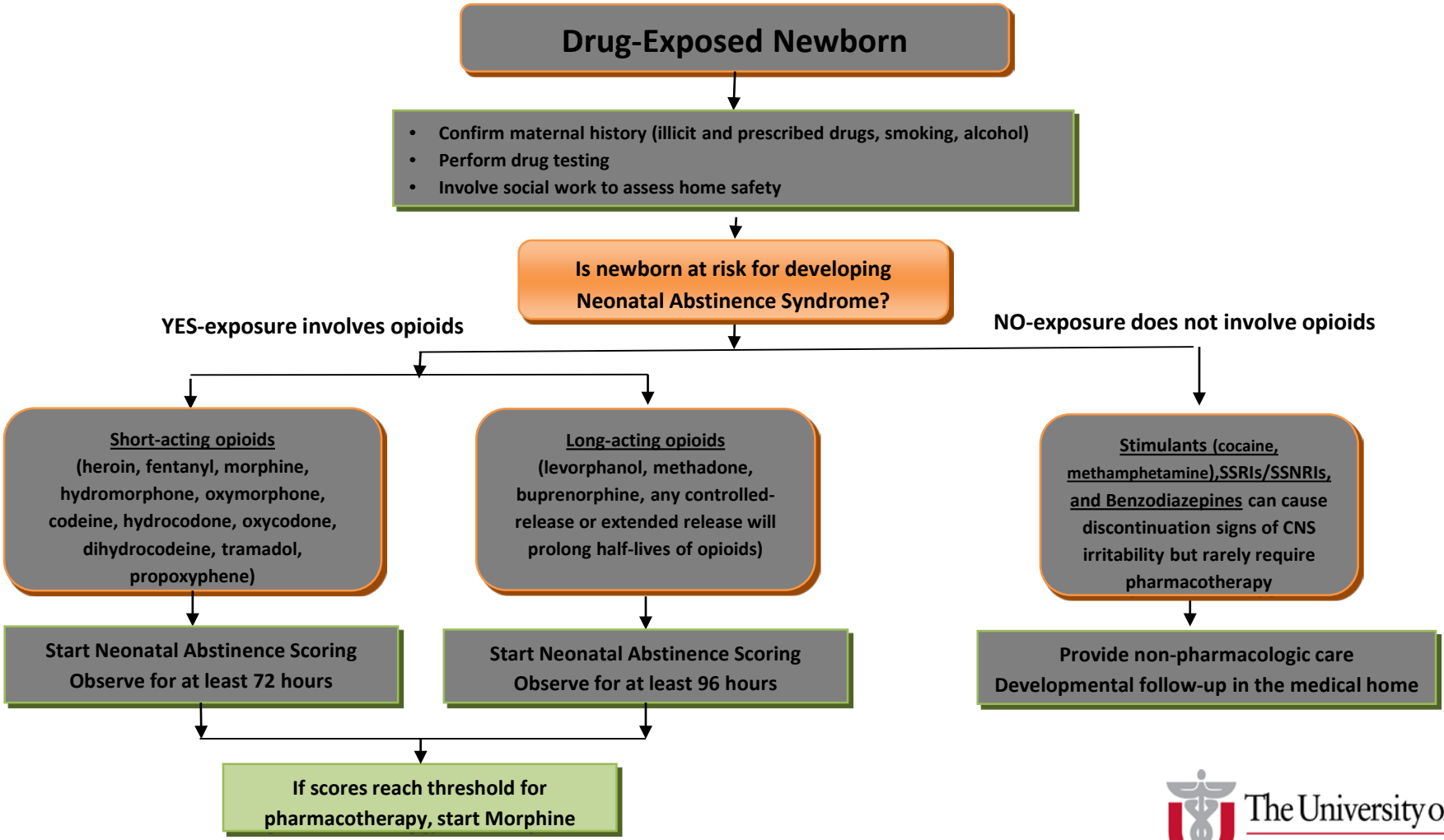
PRE-Stimulus Observation	Stimulus Observation	POST-Stimulus Observation
1 minute of observation prior to touching infant	Scoring during provision of cares, diaper change, feeding, comfort measures	1 minute of observation after cares and comfort measures completed

• Record respiratory rate
• Tremors when undisturbed (4 pts)
	• Record axillary temp (°C)
	• Tremors when disturbed (3 pts)
	• Assessment of tone
	  • Hyperactive Moro reflex (2 pts)
	  • Hypertonicity (2 pts)
	• Sweating or mottling (2 pts)
	• Regurgitation (2 pts)
	• Watery stools (2 pts)
	• Sneezing or yawning (>3 per session) (1 pt)
		• Irritability (1 pt)
		• Crying or fist-sucking (2 pts)
		• Signs of fresh excoriation of limbs (3 pts)
		• Continuous crying (4 pts)

Neonatal Withdrawal Inventory

- 11-item scoring (maximum 19 points)
- Shown to have better inter-rater reliability compared to Finnegan scoring

- Reportable scores:
- Scores 5-7
  - Reinforce non-pharmacologic care
- Scores ≥8
  - Initiate pharmacologic treatment



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NAS Treatment

Goals:

- **Relieve symptoms that are interfering with:**
  - **Physiologic stability**
  - **Feeding/Weight gain**
  - **Sleep**
  - **Ability to be consoled**

- **Improve mother-infant interactions/bonding**

Rooming In with Mother

- **Evidence that it can shorten the length of stay and reduce need for pharmacotherapy**
  - **Canada**
  - **Germany**

Saiki et al., Eur J Peds 2010; 169: 95-98
Hunseler et al., Klin Ped 2013; 225:247-251

Pharmacologic Treatment

Pharmacologic Intervention

Factors to consider

- Opiates only vs polysubstance exposure?
- Presenting with primarily CNS symptoms?
- Presenting with primarily GI symptoms?

Pharmacologic Treatment: Morphine

Morphine solution (follow dosing schedule)

- Wean if 2 consecutive scores ≤7 without GI symptoms

- If weaned according to protocol, take 8 days to complete treatment

Goal is to allow infant to eat, sleep, and gain weight

Morphine IV Weaning Schedule

Wt (g)	Level 1 0.05mg/kg	Level 2 0.045mg/kg	Level 3 0.04mg/kg	Level 4 0.035mg/kg	Level 5 0.03mg/kg	Level 6 0.025mg/kg	Level 7 0.02mg/kg	Level 8 0.015mg/kg	Level 9 0.01mg/kg	Level 10	Level 11	Level 12	Level 13
600	0.03 mg	0.03 mg	0.02 mg	0.02 mg	0.02 mg	po only	po only	po only	po only	Increase interval to q 6 dosing for at least 3 doses	Increase interval to q 8 dosing for at least 3 doses	Increase interval to q 12 dosing for at least 2 doses	Increase interval to q 24 dosing for at least 2 days
800	0.04 mg	0.04 mg	0.03 mg	0.03 mg	0.02 mg	0.02 mg	po only	po only	po only				
1000	0.05 mg	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.03 mg	0.02mg	po only	po only				
1200	0.06 mg	0.05 mg	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.02 mg	po only	po only				
1400	0.07 mg	0.06 mg	0.06 mg	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.02 mg	po only				
1600	0.08 mg	0.07 mg	0.06 mg	0.06 mg	0.05 mg	0.04 mg	0.03 mg	0.02 mg	po only				
1800	0.09 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.05 mg	0.04 mg	0.03 mg	po only				
2000	0.1 mg	0.09 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.04 mg	0.03 mg	0.02 mg				
2200	0.11 mg	0.1 mg	0.09 mg	0.08 mg	0.07 mg	0.06 mg	0.04 mg	0.03 mg	0.02 mg				
2400	0.12 mg	0.11 mg	0.1 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.04 mg	0.02 mg				
2600	0.13 mg	0.12 mg	0.1 mg	0.09 mg	0.08 mg	0.07 mg	0.05 mg	0.04 mg	0.03 mg				
2800	0.14 mg	0.13 mg	0.11 mg	0.1 mg	0.08 mg	0.07 mg	0.06 mg	0.04 mg	0.03 mg				
3000	0.15 mg	0.14 mg	0.12 mg	0.11 mg	0.09 mg	0.08 mg	0.06 mg	0.05 mg	0.03 mg				
3200	0.16 mg	0.14 mg	0.13 mg	0.11 mg	0.1 mg	0.08 mg	0.06 mg	0.05 mg	0.03 mg				
3400	0.17 mg	0.15 mg	0.14 mg	0.12 mg	0.1 mg	0.09 mg	0.07 mg	0.05 mg	0.03 mg				
3600	0.18 mg	0.16 mg	0.14 mg	0.13 mg	0.11 mg	0.09 mg	0.07 mg	0.05 mg	0.04 mg				
3800	0.19 mg	0.17 mg	0.15 mg	0.13 mg	0.11 mg	0.1 mg	0.08 mg	0.06 mg	0.04 mg				
4000	0.2 mg	0.18 mg	0.16 mg	0.14 mg	0.12 mg	0.1 mg	0.08 mg	0.06 mg	0.04 mg				
4200	0.21 mg	0.19 mg	0.17 mg	0.15 mg	0.13 mg	0.11 mg	0.08 mg	0.06 mg	0.04 mg				
4400	0.22 mg	0.2 mg	0.18 mg	0.15 mg	0.13 mg	0.11 mg	0.09 mg	0.07 mg	0.04 mg				
4600	0.23 mg	0.21 mg	0.18 mg	0.16 mg	0.14 mg	0.12 mg	0.09 mg	0.07 mg	0.05 mg				
4800	0.24 mg	0.22 mg	0.19 mg	0.17 mg	0.14 mg	0.12 mg	0.1 mg	0.07 mg	0.05 mg				
5000	0.25 mg	0.23 mg	0.2 mg	0.18 mg	0.15 mg	0.13 mg	0.1 mg	0.08 mg	0.05 mg				

Morphine PO Weaning Schedule

Wt (g)	Level 1 .075 mg/kg	Level 2 0.067mg/kg	Level 3 0.06 mg/kg	Level 4 0.053mg/kg	Level 5 0.045mg/kg	Level 6 0.037mg/kg	Level 7 0.03mg/kg	Level 8 0.023mg/kg	Level 9 0.015mg/kg	Level 10	Level 11	Level 12	Level 13
600	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.03 mg	0.02 mg	0.02 mg	0.01 mg	0.01 mg	Increase interval to q 6 dosing for at least 3 doses	Increase interval to q 8 dosing for at least 3 doses	Increase interval to q 12 dosing for at least 2 doses	Increase interval to q 24 dosing for at least 2 days
800	0.06 mg	0.05 mg	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.02 mg	0.02 mg	0.01 mg				
1000	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.05 mg	0.04 mg	0.03 mg	0.02 mg	0.02 mg				
1200	0.09 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.04 mg	0.04 mg	0.03 mg	0.02 mg				
1400	0.11 mg	0.09 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.04 mg	0.03 mg	0.02 mg				
1600	0.12 mg	0.11 mg	0.10 mg	0.08 mg	0.07 mg	0.06 mg	0.05 mg	0.04 mg	0.02 mg				
1800	0.14 mg	0.12 mg	0.11 mg	0.10 mg	0.08 mg	0.07 mg	0.05 mg	0.04 mg	0.03 mg				
2000	0.15 mg	0.13 mg	0.12 mg	0.11 mg	0.09 mg	0.07 mg	0.06 mg	0.05 mg	0.03 mg				
2200	0.17 mg	0.15 mg	0.13 mg	0.12 mg	0.10 mg	0.08 mg	0.07 mg	0.05 mg	0.03 mg				
2400	0.18 mg	0.16 mg	0.14 mg	0.13 mg	0.11 mg	0.09 mg	0.07 mg	0.06 mg	0.04 mg				
2600	0.20 mg	0.17 mg	0.16 mg	0.14 mg	0.12 mg	0.10 mg	0.08 mg	0.06 mg	0.04 mg				
2800	0.21 mg	0.19 mg	0.17 mg	0.15 mg	0.13 mg	0.10 mg	0.08 mg	0.06 mg	0.04 mg				
3000	0.23 mg	0.20 mg	0.18 mg	0.16 mg	0.14 mg	0.11 mg	0.09 mg	0.07 mg	0.05 mg				
3200	0.24 mg	0.21 mg	0.19 mg	0.17 mg	0.14 mg	0.12 mg	0.10 mg	0.07 mg	0.05 mg				
3400	0.26 mg	0.23 mg	0.20 mg	0.18 mg	0.15 mg	0.13 mg	0.10 mg	0.08 mg	0.05 mg				
3600	0.27 mg	0.24 mg	0.22 mg	0.19 mg	0.16 mg	0.13 mg	0.11 mg	0.08 mg	0.05 mg				
3800	0.29 mg	0.25 mg	0.23 mg	0.20 mg	0.17 mg	0.14 mg	0.11 mg	0.09 mg	0.06 mg				
4000	0.30 mg	0.27 mg	0.24 mg	0.21 mg	0.18 mg	0.15 mg	0.12 mg	0.09 mg	0.06 mg				
4200	0.32 mg	0.28 mg	0.25 mg	0.22 mg	0.19 mg	0.16 mg	0.13 mg	0.10 mg	0.06 mg				
4400	0.33 mg	0.29 mg	0.26 mg	0.23 mg	0.20 mg	0.16 mg	0.13 mg	0.10 mg	0.07 mg				
4600	0.35 mg	0.31 mg	0.28 mg	0.24 mg	0.21 mg	0.17 mg	0.14 mg	0.11 mg	0.07 mg				
4800	0.36 mg	0.32 mg	0.29 mg	0.25 mg	0.22 mg	0.18 mg	0.14 mg	0.11 mg	0.07 mg				
5000	0.38 mg	0.34 mg	0.30 mg	0.27 mg	0.23 mg	0.19 mg	0.15 mg	0.12 mg	0.08 mg				

Adjunctive Therapy for Neonatal Abstinence Syndrome

Predominant opioid exposure? Yes

- If morphine alone is not controlling symptoms, consider Clonidine
- Start 1mcg/kg/dose every 4-6 hours with morphine dosing
- May be increased by 0.5-1mcg/kg/dose every 24 hours to a maximum of 12 mcg/kg/day

Once morphine is weaned off

- Wean Clonidine 0.5-1mcg/kg/dose everyday.
- If infant has rebound hypertension (defined as an increase of blood pressure >95th percentile of age-specific norms), or tachycardia (>200bpm), resume previous dose for 24 hours and attempt to wean again.

Predominant opioid exposure? No

If an infant has been exposed to multiple drug classes, or has significant CNS hyperirritability, oral phenobarbital may be added.

Starting 10-20mg/kg/dose followed by 2-5mg/kg/day QD or divided BID to begin 24 hours later.

Serum phenobarbital levels are not monitored unless use is for the management of seizures. Increases in dose are not recommended as infant gains weight. Infant is allowed to outgrow the dose as symptoms wane. This is usually achieved over the first 6-8 weeks of life.

Pharmacologic Treatment: Phenobarbital

- Does not control GI symptoms
- Sometimes works better for CNS/behavioral symptoms
- Loading dose 10-20 mg/kg/dose
- Maintenance dose 2-5 mg/kg/day QD or divided BID to start 24 hours after loading
- Allow infant to outgrow dose, no need to monitor levels unless use is for seizure management

Pharmacologic Treatment: Clonidine

- Alpha-2 adrenergic agonist: presynaptic inhibitor of norepinephrine/dopamine release
- Reduces signs/symptoms while neurons reverse their tolerance to opioids
- In combination with morphine, it shortens opioid treatment for NAS

Pediatrics 2009;123:e849-e856

- Clearance increases rapidly to 70% adult rate by 1 month

J Clin Pharmacol 2011;51:502

- Single drug treatment for NAS-limited experience

Clin Toxicol 2009;47:551-5

Pharmacologic Treatment: Clonidine

- Can cause hypotension (defined as blood pressure below the 5th percentile) and bradycardia (<60bpm)
- Blood pressures and heart rates should be closely monitored prior to each dose for 24 hours after initiation or change in dosing
- Rebound hypertension and tachycardia upon weaning
- No published studies on the outpatient weaning of clonidine, therefore encourage weaning off clonidine prior to discharge

Length of hospitalization/treatment

Highly variable

- **Focus on length of sleeping periods, ability to gain weight, ability to be cared for by a "reasonable lay person"**
- **Safety of the home environment**

Breastfeeding

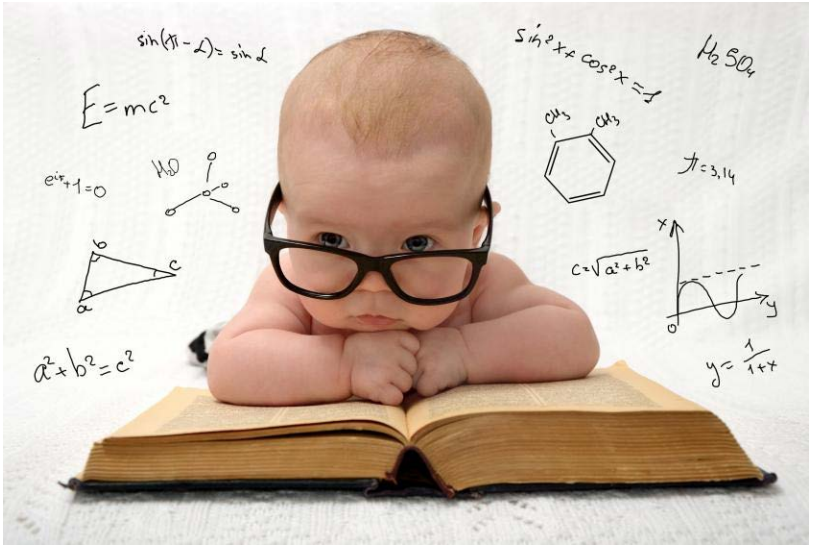
- **Check prenatal labs for infectious disease risk (HIV positivity is an absolute contraindication)**
- **Check drug screens for poly-drug use (controversy currently exists about BF with marijuana-no consensus)**
- **Safe to breastfeed with methadone/buprenorphine**
  - **Do not prevent NAS, but some studies have found it may help**
  - **Concentrations in breastmilk are low and not related to maternal dose**
    - **0.05 mg of methadone per day through the breast milk**

McCarthy and Posey J Hum Lact 2000;16(2):115-120

LactMed (http://toxnet.nlm.nih.gov)

Questions?

Feel free to reach out to me!
camille.fung@hsc.utah.edu



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