

# Utah Women and Newborns Quality Collaborative: Strategies to Improve Care for Infants with Neonatal Drug Withdrawal

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*A Resource Guide for Utah Practitioners*

# The Utah Women and Newborns Quality Collaborative Neonatal Subcommittee

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This Change Package is the product of a dedicated group of physicians, neonatal nurse practitioners, nurses, pharmacists, and administrators that represent the major healthcare systems, the State Department of Health, and specialty organizations (American College of Obstetrics and Gynecology, American Academy of Pediatrics, March of Dimes) involved with the care of women and newborns in Utah. This group of experts, known as the Utah Women and Newborns Quality Collaborative (UWNQC) Neonatal Subcommittee, was chosen for their leadership in the field of neonatology, pediatrics, and quality improvement and developed this resource over the course of two years. In the past, each hospital within the state had individual approaches to treating infants with Neonatal Drug Withdrawal. This Change Package was created to standardize a care process model for managing Neonatal Drug Withdrawal. To ensure the optimal level of care is provided to infants experiencing Neonatal Drug Withdrawal, the goals of the Neonatal Subcommittee are to decrease the length of stay for newborns requiring medications for withdrawal symptoms due to in utero substance exposure, decrease practice variation among treating practitioners, and minimize hospital costs for all Utah mothers and infants suffering from Neonatal Drug Withdrawal. UWNQC is grateful for the countless hours and expertise of all those who are involved in this project.

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## Introduction and Purpose

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Utah's perinatal quality collaborative, Utah Women and Newborns Quality Collaborative (UWNQC), was formed in 2012 with a mission to improve maternal and neonatal outcomes through collaborative efforts centered on quality improvement methodology and data sharing. As one of three UWNQC subcommittees, the Neonatal subcommittee identified Neonatal Drug Withdrawal as its initial point of emphasis in 2013. Camille M. Fung, MD, Assistant Professor in the Division of Neonatology, Department of Pediatrics at the University of Utah School of Medicine, is the Medical Director working on Neonatal Drug Withdrawal in UWNQC's Neonatal Subcommittee. Neonatal drug withdrawal includes withdrawal from opiates, classically termed neonatal abstinence syndrome (NAS), plus over-activity of the central nervous system (CNS) from discontinuation of maternal benzodiazepines, barbiturates, stimulants (cocaine, amphetamines), selective serotonin re-uptake inhibitors/serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs), marijuana, tobacco, or alcohol. These conditions have a substantial impact on the health and safety of Utah women and newborns.

From 2005-2014, according to hospital discharge data, the number of Utah newborns (birth to 28 days) diagnosed per year with NAS increased from 114 infants to 310 infants, **a 275% increase.**<sup>1</sup>

In 2011, Utah estimated total hospitalization charges associated with newborns (birth to 28 days) exhibiting drug withdrawal symptoms to be almost **\$10 million.**<sup>2</sup>

In a 2012 Utah prevalence survey, 6.8% of umbilical cord samples of 850 infants were positive for one or more substances of abuse; opiates were the most frequent (4.7%).<sup>3</sup> Extrapolated to the population, this finding suggests 2,417 newborns would test positive for opiates in 2012.

From 2012 and 2014, 1,463 Utah mothers (approximately 487 mothers per year) were reported to have used illicit drugs. As a result, **35.3% of infants** born to these mothers tested positive for illicit drugs at birth.<sup>4</sup>

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<sup>1</sup> Utah Inpatient Hospital Discharge Data, Office of Health Care Statistics, Utah Department of Health.

<sup>2</sup> Utah Department of Human Services. Division of Substance Abuse and Mental Health, 2012

Annual Report. Salt Lake City, UT: Utah Department of Human Services, Division of Substance Abuse and Mental Health. 2013.

<sup>3</sup>Buchi KF, Suarez C, Varner MW. The prevalence of prenatal opioid and other drug use in Utah. *Am J Perinatol.* 2013 Mar; 30(3):241-4. doi: 10.1055/s-0032-1323586. Epub 2012 Aug 9.

<sup>4</sup> Utah Vital Statistics: Births 2012-2014.

Each hospital in the state has had individual approaches to identify and treat newborns at risk for withdrawal. The Neonatal Subcommittee recognizes the need to standardize hospital practices to improve patient outcomes for Neonatal Drug Withdrawal. In a collaborative effort, the Neonatal Subcommittee and substance abuse teams at the University of Utah and Intermountain Healthcare established a standardized care process model (CPM) for Neonatal Drug Withdrawal.

This team has developed the following important guidelines:

- A standardized algorithm for lengths of observation based on in utero drug exposure
- Adoption of the Neonatal Withdrawal Inventory (NWI) as a tool to score signs/symptoms
- Using umbilical cords as the tissue of choice for toxicology screening through ARUP Laboratories
- Reinforcement of non-pharmacologic interventions as first-line treatment for mild withdrawal
- Reserve the use of morphine for moderate to severe withdrawal with recommended weaning parameters based on NWI scores
- Adopt early adjunctive therapy of EITHER clonidine OR phenobarbital (depending on whether the in utero exposure is predominantly opioids) to aid in morphine weaning

These resources can be found in Appendices A-E of this document.

Additionally, in January 2016, the Neonatal Subcommittee re-defined variables in the Utah Birth Certificate to collect more accurate neonatal drug withdrawal data. UWNQC is also mediating a collaborative data sharing agreement with participating hospitals to track the outcomes of this CPM.

To ensure optimal level of care is provided to infants experiencing Neonatal Drug Withdrawal, the goals of the Neonatal Subcommittee and this change package are:

- To decrease the length of stay for newborns treated with medications for Neonatal Drug Withdrawal or discontinuation symptoms
- To decrease practice variation amongst prescribers in the care of these patients
- To minimize hospital costs for all Utah mothers and infants suffering from Neonatal Drug Withdrawal

The Neonatal Subcommittee has produced this document to provide assistance to all hospitals wishing to adopt the CPM for Neonatal Drug Withdrawal. Each hospital will have unique issues to address, but there are common challenges and lessons learned that are addressed in this document.

Additional resources can be found on UWNQC's webpage  
<https://mihp.utah.gov/uwnqc/improve-neonatal-outcomes>

# Focus on Necessary Systems Changes

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## Chapter 1

**Purpose:** To smoothly transition into full integration of this CPM, hospital infrastructure changes need to be made. These adjustments will take time and coordination in the beginning, but will save time in the end.

Adjust the following:
1. Medical Record Documentation
2. Umbilical Cord Collection and Storage
3. Pharmacy Accommodations
4. Laboratory Accommodations
5. Parental Consent Process

### 1. Medical Record Documentation

- i. Documentation in medical records will need to be customized or set-up to include:
  - a. The NWI Scoring Tool (Appendix A).
    1. The tool is used during components of care. A “pre-stimulus” component is scored before the infant is handled, a “Stimulus” component is scored during provision of cares which include diaper change and feeding, and finally a “Post-stimulus” component is scored after cares are provided and infant is placed back in the crib. Each item should be displayed with its definitions in the medical record. Practitioners should pay attention to the components of the total score in addition to the total score to understand what withdrawal symptoms predominate. It is not uncommon that infants who consistently score in the “Post-stimulus” component will continue to require morphine treatment.
  - b. Medication Ordering Sets  
The medication ordering sets will include doses for morphine, clonidine, and phenobarbital. For further information, see 3 below.

## Process Hint

Plan time and support for multiple drafts where multiple people (IT specialists, pharmacists, practitioners, nurse managers) look through documentation for issues before system wide implementation. In addition, a “dry run”, where there is (1) scoring of a patient and (2) ordering appropriate medications, will show where workflow is unclear.

Large hospital systems in Utah have piloted documentation in electronic medical records (EMR) and have made customized examples available to others. Contact us for these examples.

2. Umbilical Cord Collection and Storage
  - i. Labor and Delivery will need to be consulted on the optimal process for umbilical cord collection. We advocate for universal umbilical cord collection in the event that in utero exposure is not disclosed by the mother and the infant later exhibits withdrawal. Once collected, umbilical cords must be stored in a refrigerator for up to one week. If umbilical cords are not used within one week, they can be discarded with placentae. For further information, see Chapter 2.1.
3. Pharmacy Accommodations
  - i. Ensure the correct concentrations of oral and IV morphine solutions are available for infant use. The oral formulation may need to be compounded to accommodate for the smaller volumes of doses, particularly when weaning towards the end of the morphine protocol. See Appendix B for an example of the dosing chart.
4. Laboratory Accommodations
  - i. Contact your hospital laboratory service to ensure the correct umbilical cord toxicology test can be ordered and sent to ARUP Laboratories. The test is the Drug Detection Panel by High-Resolution Time-of-Flight Mass Spectrometry using umbilical cord tissue (Test Number: 2006621), see Appendix C for additional information. Once received by ARUP, the turnaround time has been 48-72 hours. This test is performed daily.
5. Parental Consent Process
  - i. Each hospital’s parental consent process for toxicology screening of umbilical cords should be consistent with the hospital’s policy regarding newborn drug testing.



### Practice Example

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At the *University of Utah*, parental consent is not required if the newborn is showing signs/symptoms of drug withdrawal. Parental consent, on the other hand, is required if the newborn is not showing signs/symptoms of drug withdrawal.

# Re-train Quality Staff

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## Chapter 2

**Purpose:** To cultivate continuity and ensure the optimal level of care is provided to infants experiencing Neonatal Drug Withdrawal, many members of the care team will be trained. Hospitals will be prepared to obtain Neonatology consultation and/or transfer at any point when questions or concerns arise.

Train the following:
1. Staff in Labor and Delivery
2. Staff in Postpartum nurseries
3. Pharmacists

1. Staff in Labor and Delivery (L&D)
  - a. Train L&D staff for proper umbilical cord collection and storage at time of delivery.
    - i. At least 6-inches of umbilical cord will be drained of any blood, rinsed with normal saline, patted dry, and placed into a standard urine cup to be stored with patient identifier in a refrigerator for up to 1 week. The umbilical cords will be transported under cold temperature.
    - ii. Umbilical cord testing is the gold standard for drug testing. Deposition of drug/s can occur as soon as the umbilical cord is present (between 5-10 weeks gestation). Therefore, unlike meconium, which reflects 18 weeks gestation onwards of in utero exposure, umbilical cord can reflect earlier exposures. Meconium should be used as a second choice if the umbilical cord is not available.  
*Note:* Urine drug scree only reflects 24 to 48 hours of last exposure, therefore is the least useful to document longer exposure.
2. Staff in Postpartum nurseries
  - a. Train on parental consent process according to hospital policy.
    - i. Be clear what individual hospital's legal policy is on sending and reporting infant drug screens using umbilical cords.
    - ii. If the umbilical cord should be tested, this can be done by ARUP Laboratories Drug Detection Panel by High-Resolution Time-of-Flight Mass Spectrometry using umbilical cord tissue (Test Number: 2006621, See Appendix C for additional information). Results are available in approximately 48-72 hours. Testing occurs daily.  
*Note:* Umbilical cord tissue testing is a qualitative, not a quantitative test which means that it will detect the presence or absence of drugs in the umbilical cord. Certain drugs including cocaine or buprenorphine can be difficult to extract from the umbilical cord. Therefore, if these

drugs are suspected in the maternal history, yet none are detected in the cord, please contact an ARUP pathologist to clarify the detection cutoff levels (801-583-2787 or 800-522-2787).

- b. Train on verifying maternal drug exposures.
  - i. Ascertainment of maternal exposure information is accurate to anticipate necessary pharmacological intervention if the infant becomes symptomatic.
  - ii. A mother may not fully disclose her drug use. Ask in a non-judgmental manner and focus on improving infant's withdrawal symptoms as the goal.
  - iii. Do not forget nicotine use that may exist in other forms such as nicotine patch, nicotine gum, or e-cigarettes in addition to traditional cigarettes. Nicotine is also a central nervous system stimulant.

### State Resource

Supported through the Utah Department of Health, *Way to Quit*, is a free cessation program with resources including a 24-7 phone line, mobile texting, and online coaching all free of charge. Visit [waytoquit.org](http://waytoquit.org) for additional information.

- c. Train on EMR
  - i. For nurses who will be assessing the infant and entering the NWI scores, it is recommended that champion nurses are identified who can gain expertise in this process. They can then be responsible for training other nurses to ensure consistency and accuracy of scoring. Make sure each score is reported to practitioners so appropriate next steps can be made.
  - ii. For any medical staff provider who is managing withdrawal medication therapy, it is important to be familiar with both how to wean and how to escalate medications based upon the NWI scores. On the EMR ordering set, before the next morphine level dose is ordered, ensure the previous morphine level dose is discontinued. When withdrawal is severe and it appears that morphine is insufficient to manage symptoms, adjunctive therapy with clonidine or phenobarbital may be appropriate.
- d. Train on scoring tool.
  - i. The NWI is the gold standard in Neonatal Withdrawal Care Process Model. Other scoring tools, such as the Finnegan<sup>a</sup> scoring tool or Lipsitz<sup>b</sup> scoring scale, have traditionally been used in hospitals. The NWI is scored similarly to Finnegan scoring therefore transition to the NWI will be fairly straightforward. In the original study, the NWI was shown to have better interrater variability than the Finnegan because of its ease of use<sup>c</sup>.

a. Finnegan, L. P., Connaughton, J. F., Kron, R. E., & Emich, J. P. (1975). Neonatal abstinence syndrome: assessment and management. *Addict Dis*, 2(1-2), 141-158.

b. Lipsitz, P. J. (1975). A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. *Clin Pediatr (Phila)*, 14(6), 592-594.

c. Zahorodny, W., Rom, C., Whitney, W., Giddens, S., Samuel, M., Maichuk, G., & Marshall, R. (1998). The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *J Dev Behav Pediatr*, 19(2), 89-93.

- ii. It is important to include pharmacists as team members who can make dosing change recommendations based on NWI scores.
- e. Train on soothing techniques.
  - i. Ensure staff know the non-pharmacologic comfort measures that could be attempted to sooth the infant. These include low lighting, gentle rocking, minimizing environmental noise, C-shaped holds, use of a pacifier, nesting/swaddling with soft blankets, side-lying positions, and skin-to-skin contact.
  - ii. Minimize over-feeding even though these infants may act hyperphagic. We also do not advocate high caloric density feeding if the infant is gaining weight appropriately as this may precipitate diarrhea.
  - iii. Teach parents/caregivers what soothing techniques work for their infants. Even though the infants have weaned off their medications successfully in the hospital, they may still exhibit mild symptoms of withdrawal after discharge. Therefore, non-pharmacologic interventions should be taught to parents.
  - iv. Infants greater than 2 to 4 weeks old may require more developmental stimulation than simply laying in a darkened, quiet room. Consider involving developmental specialists to design an age-appropriate interaction that does not over-stimulate these vulnerable infants.
- 3. Pharmacists
  - a. Pharmacists may need to work with their hospital formularies to obtain the correct concentration of morphine solution needed for oral administration in these infants. The same issue may apply to clonidine solution for infant use. See Appendix B for an example of the dosing chart.

#### Process Hint

Prior experiences have revealed that various hospitals carry different concentrations of morphine solution such that when small volumes are needed toward the end of the morphine weaning schedule, administration becomes an issue. Make sure these concentrations are available.

- b. Pharmacists should feel EMPOWERED to make dosing change recommendations to practitioners based on NWI scores. If a practitioner is not compliant with the treatment protocol, i.e. when an infant is eligible to wean to the next level based on 2 consecutive scores  $\leq 7$  without GI symptoms, a justification must be sought as to why morphine is not weaned.

### Process Hint

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The Neonatal Drug Withdrawal Care Process Model should be worked into the orientation of new hires. Process champions should be identified at every level to ensure consistent onboard training.

# Provide Exceptional Compassionate Clinical Care

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## Chapter 3

**Purpose:** To ensure the optimal level of care is provided to infants experiencing Neonatal Drug Withdrawal, many other team members will be included beyond the direct-staff. Process champions will be identified to help with these trainings and be available when questions arise.

Involve the following:
1. Family Members
2. Process Champions
3. Social/Case Workers
4. Developmental Specialists/Occupational and/or Physical Therapists
5. Pediatricians

1. Family Members
  - a. During their infant's hospitalization, family anxiety is reduced when they know clinicians are moving through a treatment algorithm aimed to reduce length of hospitalization.
  - b. Teach families the non-pharmacologic interventions that work for their particular infant. Be mindful that infants who required pharmacological interventions to treat their severe withdrawal symptoms may still exhibit periods of irritability and fussiness after hospital discharge as the central nervous system continues to normalize. Therefore, it is vital that families know what non-pharmacologic maneuvers are effective for their infant.
2. Process Champions
  - a. At each level (L&D & postpartum nurses, mid-level providers, practitioners and pharmacists, etc.) will be identified. This is particularly important at the initial roll-out phase to ensure that consistency and compliance are maintained. See Chapter 2 for examples of the roles these process champions will have.
3. Social/Case Workers
  - a. Dedicated social workers or case workers who have experience working with families of infants with NAS and are knowledgeable about Utah's reporting requirements are vital. Involve them early in the hospitalization. They can play an essential role in identifying risk factors that may be unsafe for infant discharge. They can also assist in referring mothers for psychiatric support and substance abuse programs.
4. Developmental Specialists/Occupational and Physical Therapists
  - a. This is strongly encouraged at any time but particularly as the infant stays beyond 2-4 weeks of life.

## 5. Pediatricians

- a. Pediatricians who will be following these infants on an outpatient basis should be notified and be involved before an infant's discharge. The pediatrician may already have an established relationship with the mother and family if they care for their other older children.
- b. Ensure that if an infant is sent home on medications, pediatricians are comfortable with the management and discontinuation. Please note that our treatment algorithm DOES NOT recommend home discharge with oral clonidine, as no literature exists on the optimal weaning as an outpatient. If an infant is to be sent home on oral clonidine, an explicit weaning strategy must be discussed with the outpatient pediatrician. The risk of sending an infant home on weaning clonidine is rebound hypertension and tachycardia which are not detected unless the infant is continuously monitored.

# Be a Continuous Learning Organization

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## Chapter 4

**Purpose:** To reduce variations in care and improve performance, organizations will be willing and ready to make changes as needed.

Plan on the following:	
	1. Reach Out as Questions Arise
	2. Track Progress
	3. Look for Resources

1. Reach Out as Questions Arise
  - a. Expertise on NAS is abundant within UWNQC, feel free to reach out to UWNQC when questions arise. To do this, follow this link: <http://health.utah.gov/uwnqc/contact.html>.
2. Track Progress by Data Reporting
  - a. In order to assess the decrease in length of stay for newborns requiring medications for withdrawal symptoms due to in utero substance exposure, the decrease in practice variation of these patients, and the minimization of hospital costs for all Utah mothers and infants suffering from Neonatal Drug Withdrawal, it is imperative to properly track these outcomes. Hospitals will need to work within their teams to decide the best way to do this. Due to factors relating to the diagnosis of NAS, the use of multiple classes of drugs prenatally, the difficulty of abstracting data from medical records, etc., it has proven challenging to get accurate statewide data. To track our progress of the Neonatal Withdrawal CPM, we are asking individual hospitals to enter data into our UWNQC REDCAP database. Through collaborative efforts, we will be able to ensure that the best care process is administered to this high-risk cohort of infants.
    - i. REDCap is a mature, secure web application for building and managing online surveys and databases. If your hospital is willing to provide de-identified, aggregate numbers, please contact us.
3. Resources.
  - a. Additional resources can be found on UWNQC's webpage [http://health.utah.gov/uwnqc/pages/neonatal\\_resources.html](http://health.utah.gov/uwnqc/pages/neonatal_resources.html).



## Appendix A

**Instructions for Use :** Scoring should begin when it has been determined that the infant demonstrates signs and symptoms of withdrawal, then repeated every 3 to 4 hours. If the infant's total score is 8 or greater, the assessment should be repeated every 2 to 3 hours until a total score of 7 or less is obtained over a 24 hour period. At this time, every 3 to 4 hour scoring may be resumed.

## Assessment Procedures for the Neonatal Withdrawal Inventory

<b>PRE-Stimulus Observation (1 minute)</b>	<ul style="list-style-type: none"> <li>• Tremors when undisturbed</li> <li>• Respiratory Rate</li> </ul>
<b>Stimulus Observation</b>	<ul style="list-style-type: none"> <li>• Assessment of tone and Moro reflex</li> <li>• Tremors when disturbed</li> <li>• Sweating or mottling</li> <li>• Axillary temperature</li> <li>• Sneezing or yawning</li> <li>• Loose, watery stools</li> <li>• Reswaddle and position</li> </ul>
<b>POST-Stimulus Observation (1 minute)</b>	<ul style="list-style-type: none"> <li>• State (irritability, crying, fist-sucking, signs of excoriation, continuous crying)</li> </ul>
<b>Reportable Condition</b> = score of 5 or higher. Use non-pharmaceutical interventions for score of 5 to 8. Pharmaceutical interventions suggested for score of 8 or higher.	

[illegible]

## Assessment Procedure for Neonatal Withdrawal Inventory

- Observe infant, undisturbed in his/her bassinet, for 1 minute
- Unswaddle and gentle awakening (if necessary)
- Determine respiratory rate when calm
- Measure axillary temperature
- Inspect limbs and extremities for recent excoriation
- Assess muscle tone and Moro reflex
- Feed / change diaper
- Re-swaddle and position for comfort
- Observe the infant for 1 minute without intervention

Choose One	Tremors when Disturbed	Score if tremors are present after the infant has been disturbed by noise or handling.
	Tremors when Undisturbed	Score if tremors are present when the infant is asleep or at rest in the bassinet.
	Hypertonicity	Score if excessive or above-normal muscle tone or tension is observed. <i>Example: muscles become "stiff" or rigid and the infant shows marked resistance to passive movement-no head lag when pulled to sitting position, tight flexion of the arms and legs, or resists attempts to extend.</i>
	Hyperactive Moro	The Moro or startle reflex is normal in young infants. Score if infant exhibits pronounced jitteriness or repetitive involuntary jerks of the hand and or arms during or after the initiation of the Moro reflex.
	Sneezing or Yawning	Score if more than 3 sneezes and/or yawns are observed within the scoring interval.
	Sweating or Mottling	Score if sweat is spontaneous and not due to excessive clothing or high room temperature. Score if mottling ( <i>marbled appearance of pink and pale or white areas</i> ) is present on the infant's chest, trunk, arms, or legs and the infant is not cold.
	Regurgitation	Score if at least one episode of regurgitation is observed.
	Watery Stools	Score if watery stools (defined as no solid substance or >3 stools in a 3-hour period) are observed with the diaper change.
Choose One	Irritability	Score if infant remains restless even after intervention.
	Crying or Frantic Fist-Sucking	Score if infant displays intermittent crying or frantic fist-sucking despite completing feeding.
	Fresh Excoriation of Limbs	Score only when excoriations first appear, increase, or appear in new area.
	Continuous Crying	Score if infant is unable to calm despite comfort measures.

## IV Dosing - NAS Morphine Weaning Schedule - IV Dosing

Wt	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8	Level 9	Level 10	Level 11	Level 12	Level 13
(grams)	0.05mg/kg	0.045mg/kg	0.04mg/kg	0.035mg/kg	0.03mg/kg	0.025mg/kg	0.02mg/kg	0.015mg/kg	0.01mg/kg				
600	0.03 mg	0.03 mg	0.02 mg	0.02 mg	0.02 mg	po only	po only	po only	po only				
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	0.02 mg	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	0.10 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	0.10 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	0.10 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	0.10 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	0.10 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	0.10 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	0.10 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	0.10 mg	0.08 mg	0.06 mg	0.04 mg				
4000	0.20 mg	0.18 mg	0.16 mg	0.14 mg	0.12 mg	0.10 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	0.20 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	0.10 mg	0.07 mg	0.05 mg				
5000	0.25 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				
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 24 hrs													

## PO (Oral) NAS Morphine Weaning Schedule

Wt	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7	Level 8	Level 9	Level 10	Level 11	Level 12	Level 13
(grams)	0.075 mg/kg	0.067 mg/kg	0.06 mg/kg	0.053mg/kg	0.045mg/kg	0.037 mg/kg	0.03mg/kg	0.023mg/kg	0.015mg/kg				
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				
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				
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													

# Drug Detection Panel by High-Resolution Time-of-Flight Mass Spectrometry, Umbilical Cord Tissue

## Indications for Ordering

- Detect prenatal exposure to drugs in umbilical cord tissue for infants
  - Born to mothers with high risk (eg, history of drug use, prostitution, sexually transmitted disease)
  - Born to mothers with little or no prenatal care
  - Born to mothers with unexplained placental abruption or premature labor
  - Born with unexplained neurological complications
  - Born with unexpected intrauterine growth retardation
  - Born with evidence of intoxication and/or drug withdrawal symptoms
- Order as an alternative to meconium screening, or when meconium is not available

## Test Description

- Reverse phase liquid chromatography coupled with high resolution accurate time-of-flight mass spectrometry (LC/TOF-MS) and enzyme-linked immunosorbent assay
- Qualitative detection of drugs/drug metabolites (see table below for list of drugs covered and ranges of cutoff)
- **At least 6 inches of umbilical cord is required**
  - Drain and discard any blood
  - Rinse the exterior of the cord segment with normal saline or an equivalent
  - Pat the specimen dry and place in container (standard urine cup)
  - Transport refrigerated
- Confirmation testing usually not required due to specificity of technology employed (high resolution, accurate mass spectrometry)

## Tests to Consider

### Primary test

[Drug Detection Panel by High-Resolution Time-of-Flight Mass Spectrometry, Umbilical Cord Tissue 2006621](#)

- Qualitative detection of drugs and drug metabolites to assess prenatal drug exposure
- Alternative to meconium screening

## Disease Overview

### Screening/detection

- Timely detection of in-utero drug exposure is critical for effective detection and management of intoxications, withdrawal syndrome, and long-term needs (social and medical) for exposed neonates
  - Actual time window for detecting exposure is unknown, but is thought to represent at least the last trimester
- Detection of drugs depends on
  - Extent of maternal drug use
  - Drug stability
  - Deposition of drug analytes in umbilical cord tissue
  - Performance of the analytical method
- Umbilical cord tissue testing may be preferable to meconium due to
  - Ease of collection of a larger volume of specimen
  - Relatively fast turnaround time
  - Reflex/confirmation testing typically not required

### Test Interpretation

#### Sensitivity/specificity

- Clinical sensitivity – consistent with detection of compounds and metabolites in meconium testing
- Clinical specificity – high
  - Antibody-based method reduces false positives and the need for confirmatory testing

#### Results

- Positive – drug analytes detected in umbilical cord tissue
  - Consistent with exposure to the relevant drug(s) prior to birth
  - Does not insinuate impairment and may not affect outcomes for the associated infant
  - Drugs administered during labor and delivery may be detected
- Negative – drug analytes absent in umbilical cord tissue
  - Does not exclude the possibility that the mother used drugs during pregnancy

#### Limitations

- Details regarding the specific formulation, amount/dose, or time and length of exposure cannot be established by this testing

- Minimum reporting limits (ng/g, pg/g) are established for each compound (see table below), but quantitation of detected drugs is not performed
- Deposition of drugs in umbilical cord is not identical to meconium
  - Concentrations of drugs and metabolites in cord tissue are generally lower than those found in meconium
- This test is qualitative and does not provide quantitative results
- While testing may be performed with chain of custody, ARUP is not a forensic laboratory; this test is intended for clinical use

Drugs/Drug Classes	Range of Cutoff
<b>Opioids</b>	
Buprenorphine, codeine, fentanyl, heroin (6-acetylmorphine), dihydrocodeine, hydrocodone, hydromorphone, meperidine, methadone, morphine, naloxone, naltrexone, oxycodone, oxymorphone, propoxyphene, tapentadol, tramadol	1-10 ng/g
<b>Stimulants</b>	
Amphetamines, cocaine, methamphetamine, MDMA, MDEA, MDA, phentermine	8 ng/g
<b>Sedative-hypnotics</b>	
Alprazolam, butalbital, clonazepam, diazepam, flunitrazepam, flurazepam, lorazepam, midazolam, nitrazepam, nordiazepam, oxazepam, phenobarbital, secobarbital, temazepam, triazolam, zolpidem	5-75 ng/g
<b>Phencyclidine (PCP)</b>	
PCP	4 ng/g
<b>Cannabinoids (11-nor-9-carboxy-THC)</b>	
THC	150 pg/g
<b>Note:</b> Some drugs are identified based on the presence of unique drug metabolites that are not listed above	

## Drug-Exposed Newborn or Unknown Exposure but Infant Showing Withdrawal Symptoms

- 1) Confirm maternal history (illicit and prescribed drugs, smoking, alcohol)
- 2) Send umbilical cord for testing<sup>1</sup>  
If cord unavailable, send meconium<sup>2</sup>
- 3) Involve social work to assess home safety

Is newborn at risk for developing NAS / discontinuation syndrome?

YES - exposure involves

YES - exposure excludes opioids

### Short-acting opioids

(heroin, fentanyl, morphine, hydromorphone, oxymorphone, codeine, hydrocodone, oxycodone, dihydrocodeine, tramadol, propoxyphene)<sup>3</sup>

Start Neonatal Withdrawal Inventory scoring when symptoms arise (refer to scoring sheet and treatment algorithm).  
Recommend Observation for at least 72 hours from time of birth<sup>6,7</sup>

### Long-acting opioids

(methadone, buprenorphine, levorphanol, any controlled-release or extended release will prolong half-lives of opioids)<sup>3</sup>

Start Neonatal Withdrawal Inventory scoring when symptoms arise (refer to scoring sheet and treatment algorithm).  
Recommend Observation for at least 96 hours from time of birth<sup>6,7</sup>

### Stimulants (cocaine, methamphetamine), marijuana, SSRIs/SSNRIs

can cause discontinuation signs of CNS irritability but rarely require pharmacotherapy<sup>4,5</sup>

Start Neonatal Withdrawal Inventory scoring when symptoms arise (refer to scoring sheet).  
Recommend Observation for at least 72 hours from time of birth<sup>5,6</sup>

If one week or longer has elapsed between the last maternal opioid use and delivery of infant, the incidence of NAS is relatively low<sup>7</sup>.

In addition to opioids, does exposure include other drugs that affect the CNS such as nicotine, benzodiazepines, marijuana, SSRIs/SSNRIs/anti-seizure?

Yes

May have more significant CNS withdrawal symptoms that require longer observation<sup>6,8</sup>

## Adjunctive Therapy for Neonatal Abstinence Syndrome

Predominant opioid exposure? Yes<sup>11,12</sup>

If infant cannot progress to the next morphine level of treatment at any level, oral clonidine should be considered.

Start 1.5 mcg/kg/dose every 6 hours to be given with morphine dose<sup>12,13,14</sup>. May be increased by 2 mcg/kg/day Q24h to a maximum of 12 mcg/kg/day<sup>12,13,14</sup> if severity of withdrawal does not improve. Always use the weight at initiation for dose increase\*\*.

Once morphine is weaned off

Wean daily dose by half every day over the next 2 days and then discontinue on 3<sup>rd</sup> day<sup>14,15</sup>. Always use weight at initiation for dose decrease. If infant has rebound hypertension or tachycardia\*\*, resume previous dose for 24 hours and attempt to wean again.

### \*\*Important note to consider

Clonidine is an alpha-2 adrenergic agonist, therefore can cause hypotension (defined as blood pressure <5<sup>th</sup> percentile for age) and/or bradycardia (<60bpm). On the converse when weaning, can cause rebound hypertension (defined as blood pressure >95<sup>th</sup> percentile) and/or tachycardia (>200bpm), therefore monitor BP and HR Q6h.

No published studies exist on the optimal outpatient weaning of clonidine, therefore we discourage discharging infants home on clonidine.

Note: A conversation with infant's pediatrician is vital to ensure adequate follow-up if infant is to be sent home on clonidine.

Predominant opioid exposure? No

If infant has been exposed to multiple drug classes and has significant CNS symptoms, oral phenobarbital should be considered.

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

Phenobarbital works well for CNS symptoms but NOT for GI symptoms (you need morphine for the latter). No need to measure serum phenobarbital level unless for seizure management. Infants can be discharged home with phenobarbital and be allowed to outgrow their dose, usually takes the first 6-8 weeks of life.

### TO BREASTFEED OR NOT?

Breastfeeding is generally recommended for mothers of babies with NAS unless risks outweigh benefits<sup>16</sup>. Mothers on methadone or buprenorphine should be encouraged to breastfeed unless there is ACTIVE illicit substance use, at which time mothers should be counseled on risks with active use<sup>16</sup>.

*Generally accepted contraindications to breastfeeding are HIV+/AIDS, herpes lesion on breast, active TB, human T-cell lymphocytic virus, radioactive isotope or antimetabolite exposure<sup>16</sup>.*

Refer to AAP Clinical Report on "The Transfer of Drugs and Therapeutics into Human Breast Milk: An Update on Selected Topics" for guidance if you have any questions about safety of medications in breastmilk<sup>10</sup>.

NIH also maintains an updated database (LactMed) on information of drugs and chemicals on breastfeeding mothers. All data derived from scientific literature and fully referenced.

(<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>)



# Management of Neonatal Abstinence Syndrome involving Opioids (MAJOR GOAL: to promote normal patterns of sleeping, feeding, and weight gain)

Neonatal Withdrawal Inventory Score  
(normally scored every 3-4 hours based on feeding intervals)

If scores  $\leq 7$

If 2 consecutive scores  $\geq 8$ , or *persistent* vomiting or watery stools (defined as no solid substance or  $>3$  every 3 hours) with any score

Reinforce non-pharmacologic maneuvers (reduce stimulation with quiet and low-lighted room, nesting/swaddling with soft blankets, side-lying position, C-shaped hold, sucking on pacifier, skin-to-skin contact, gentle rocking).

Start at Level 5 dosing if scores  $\leq 7$  **but** have persistent vomiting/watery stools.

Start oral morphine sulfate at Level 1 dosing (Use the NAS order set in EMR to order morphine. Use BIRTH WEIGHT for dosing every time. Do NOT modify pre-set dosages. Just choose dose at level 1, or level 2, or level 3, etc.). If infant cannot take oral formulation, consult NICU for I.V. morphine. Start I.V. dose at the level you would for oral dose but use I.V. dosing schedule.

Infant scores  $\leq 7$  on 2 consecutive scoring. [Note: If *persistent* vomiting/watery stools after Rx, morphine should NOT be weaned regardless of score.]

Infant scores  $\geq 8$  on Level 1 dosing. [Note: *May need to score/treat hourly to get symptoms controlled at onset, then score/treat based on feeding intervals after stabilization.*]

Wean morphine dose to Level 2 (give lower dose on the 9<sup>th</sup> hour if Q3h feeding).

Give an additional Level 1 dose. Consider adjunctive therapy if morphine is insufficient. Consult NICU if at a level II (A or B) nursery.

Infant scores  $\leq 7$  on 2 consecutive scoring. Assess vomiting/watery stools.

Infant scores  $\geq 8$  on 2 consecutive scoring.

Consider adjunctive therapy at any level when you are unable to progress through levels.

Wean morphine dose to next level. Keep weaning as long as 2 consecutive scores  $\leq 7$  without persistent vomiting/watery stools.

Infant scores  $\geq 8$  on 2 consecutive scoring.

Return to the previous level of dosing.

If infant was started on I.V. morphine due to N.P.O. status, to convert to oral morphine when ready, use the weight appropriate level of dosing to convert. For example, a 3kg infant is on I.V. morphine at Level 4, oral morphine should be converted to level 4 dose for a 3kg infant. IV dose  $\neq$  po dose

From Level 10 to 13, morphine interval is progressively increased (coordinate Rx with feeding schedule)<sup>9</sup>.

Scoring and dosing must be done for a minimum of 24 hours at Levels 11 and 12, and a minimum of 48 hours at Level 13.

Keep track of infant's weight gain and sleep pattern to determine optimal time of discharge. Earliest discharge is the next day after finishing level 13 dosing, i.e. on the 3<sup>rd</sup> day after starting level 13. May keep infant longer if there are

## Footnotes for NAS Algorithms

- <sup>1</sup>Send Drug Detection Panel by High-Resolution Time-of-Flight Mass Spectrometry, Umbilical Cord Tissue 2006621; at least 6 inches of umbilical cord is required; this is a qualitative detection of drugs and drug metabolites to assess prenatal drug exposure.
- <sup>2</sup>Need at least a gram of meconium; reflects exposure since 18 weeks of gestation; MORE IMPORTANT than a newborn urine specimen.
- <sup>3</sup>Argoff et al. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain. *Mayo Clinic Proc* 2009; 84:602-612.
- <sup>4</sup>Moses-Kolko et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; 293(19):2372-2383.
- <sup>5</sup>Ferreira et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007; 119:52-59.
- <sup>6</sup>Jansson et al. Neonatal abstinence syndrome. *Curr Opin Pediatr* 2012; 24(2):252-258.
- <sup>7</sup>AAP Clinical Report: Neonatal Drug Withdrawal. [www.pediatrics.org/cgi/doi/10.1542/peds.2011-3212](http://www.pediatrics.org/cgi/doi/10.1542/peds.2011-3212).
- <sup>8</sup>Iqbal et al. Effects of commonly used benzodiazepines on the fetus, the neonate and the nursing infant. *Psychiatr Serv* 2002; 53:39-49.
- <sup>9</sup>From level 10 to 13, practitioners can consider weaning faster or slower by increasing or decreasing interval between doses based on infant's NWI scores, weight gain, and sleep pattern.
- <sup>10</sup>AAP Clinical Report: The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. [www.pediatrics.org/cgi/doi/10.1542/peds.2013-1985](http://www.pediatrics.org/cgi/doi/10.1542/peds.2013-1985).
- <sup>11</sup>Broome et al. Neonatal Abstinence Syndrome: The use of clonidine as a treatment option. *Neoreviews* 2011; 12:e575-e583.
- <sup>12</sup>Agthe et al. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized controlled trial. *Pediatrics* 2009; 123(5):e849-e856. [Note: this is the only randomized controlled trial using clonidine as an adjunctive therapy to opioid exposure. Therefore we have opted to use clonidine as an adjunct to pure opioid exposure rather than to polysubstance abuse.]
- <sup>13</sup>Broome et al. Neonatal Abstinence Syndrome: The Use of Clonidine as a Treatment Option. *Neoreviews* 2011; 12(10):e575-e584. [This is a good historical review on what clonidine doses have been tried in the past.]

## Appendix E

### References in support of this CPM *plus additional reading*

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