

## **NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS) CLINICAL GUIDELINES**

**Indications for use of these guidelines:** Infants chronically exposed to opioid medications *in-utero* such as methadone, buprenorphine (Subutex or Suboxone), morphine, oxycodone, hydromorphone, and heroin. NOWS is also known as Neonatal Abstinence Syndrome (NAS).

**Inpatient monitoring for NOWS:** Methadone and buprenorphine exposed infants should be monitored in the hospital for a minimum of **5-7 days** for signs of withdrawal.

**Vivitrol (extended-release naltrexone) or oral naltrexone:** This is newer option for treatment of opioid use disorder in pregnancy. It is not an opioid medication. Infants exposed to naltrexone do not require monitoring for NOWS. These mother-infant dyads should receive a social work consultation and maternal toxicology testing per L&D policy. They should be referred to the SO FAR clinic and/or Baby Steps, but do not require Ophthalmology follow-up or an Early Intervention referral. Breastfeeding is permitted for individuals who are stable on extended-release naltrexone. Page Elisha Wachman or Kelley Saia with further questions.

**NOWS Risk Factors:** 40-50% of exposed infants are treated with medication for NOWS at BMC

- **Increased risk:** Methadone; concurrent medications including benzodiazepines and SSRIs; nicotine; poly-pharmacy exposure
- **Decreased risk:** Breastfeeding; prematurity; buprenorphine; short-acting opioids

### **Goals of Treatment:**

- Decrease irritability; optimize ability to interact with environment
- Normalize feeding; minimize diarrhea and vomiting; provide adequate nutrition
- Promote sleep (>2 hours between feeds), but do not heavily sedate infant
- Involve family in care, as appropriate, or work with DCF to identify foster care as early as possible

### **Non-Pharmacologic Treatment: *All infants should receive these interventions as first-line treatment***

- Skin-to-skin holding with parents as often as possible
- Encouragement of parental presence at the bedside as often as possible
- Decreased stimulation (light and voice)
- Cluster care to avoid unnecessary wakings between feeds
- Swaddling and sleep sacks
- Pacifier

### **NOWS admission orders and consultations:**

- Please give **NAS parent brochure** and **NAS bundle of care handout** upon admission
- See NOWS computerized order set: "NAS/NOWS" or "NICU NAS/NOWS"
  - o NOWS "ESC" assessments every 3-4 hours (*see below*)
  - o Similac Advance 20 formula if not breastfeeding (*see below*)
- Consults:
  - o Social Work, Occupational Therapy, and Nutrition for all infants
  - o Lactation for breastfeeding babies
  - o Pediatric ID consult if mom HIV positive or Hepatitis C positive
  - o Project RESPECT pager 2593 **Monitoring and Scoring:**

- Infants should be assessed while in the parent's postpartum room, and can be assessed skin-to-skin on the parent
- For infants  $\geq 34$  weeks GA, the decision to treat should be based on the **Neonatal Opioid Syndrome Assessment Tool "ESC"**. For infants  $< 34$  weeks, the **NICU Withdrawal Assessment Tool (NWAT)** should be utilized for assessments. Please see **Neonatal Opioid Withdrawal Syndrome Algorithm** for guidelines for pharmacotherapy.
- Infants on methadone therapy do not require a baseline EKG. There is no reported risk for prolonged QTc with this dosing in neonates. Consider EKG and/or consult pediatric pharmacy if infant is on other medications known to prolong the QTc. If an EKG is obtained for other clinical reasons and the QTc is  $>500$ ms, please consult with pediatric pharmacy and hold methadone.
- **Vital sign monitoring for infants on PRN or standing methadone:**
  - o Infants do not require continuous cardiorespiratory or oximetry monitoring. PRN or standing methadone may be given in the postpartum room.
  - o Check infant vital signs (**HR and RR**) prior to giving dose of **PRN or standing methadone**: If HR  $< 80$  or RR  $< 20$ , please consult with the nursery attending prior to giving.
  - o The infant should have **hourly HR and RR checks** in the postpartum room until **4 hours** after the first methadone dose. If the dose is tolerated well with no apnea or bradycardia events, the infant should then have vital signs every 8 hours for the duration of methadone treatment.
  - o Criteria to be placed on a continuous monitor in the nursery include, *but are not limited to*:
    - Apnea or hypopnea (RR  $< 20$ ) (*defined as  $>20$  second pause in breathing, or any apnea with desaturation  $< 85\%$* )
    - O2 sat  $< 93\%$
    - HR consistently  $< 80$ . *Infants with transient HRs to the 70's that self-resolve can be discussed with the nursery attending on a case by case basis.*

#### **Nutrition:**

- Breastfeeding should be encouraged for methadone and buprenorphine exposed infants who meet eligibility criteria. See **Breastfeeding with Prenatal Substance Use Guidelines**.
- Use **Similac Advance 20 formula** for all infants who are opioid exposed, symptomatic and/or IUGR if the mother chooses not to breastfeed, is unable to breastfeed, stops breastfeeding or when supplementing breastfeeds. Nutrition should be consulted.

#### **Toxicology Testing for Infants:**

- The goal of toxicology testing is to help guide the medical management of the infant.
- **Indications for obtaining a urine toxicology test on the infant:**
  - o Symptoms consistent with CNS irritability including seizures or signs and symptoms of neonatal substance withdrawal of unknown etiology affecting management of the infant,.
  - o Known maternal substance use disorder during pregnancy in which there is no maternal toxicology test obtained on Labor and Delivery
- **Indications for obtaining a meconium toxicology test:**
  - o Meconium toxicology testing is not routinely recommended at BMC
- **Consent:**

- Parental consent is not required for a toxicology testing if any of the above indications are met
- The pediatric provider must meet with the parent(s) to explain the reasons for the sample collection and the possible consequences associated with positive test results for non-prescribed substances (e.g., notification to DCF).
- Upon completion of the testing, the provider should meet with parent(s) again to discuss the results of the testing and the plan for the infant.
- What to order when sending a toxicology test:
  - Urine toxicology test “Basic screen” (amphetamines, barbiturates, benzodiazepines, cocaine metabolites and opiates)
  - Urine “Expanded opioid panel” (buprenorphine, methadone, oxycodone, fentanyl)
  - *Note: It is not recommended to screen for marijuana (THC) due to unreliability*
  - *Note: Epidural fentanyl may interfere with maternal or infant toxicology testing results*

**Guidelines for NPO Patients:** First line therapy is IV morphine: See **Appendix A** on the [Neonatal Opioid Withdrawal Syndrome Algorithm](#) for dosing guidelines.

**Circumcision Timing:**

- Circumcisions can be done at any point after the first 24 hours of life, either while the infant is still on the Mother Infant Unit or after transfer to Yawkey 5 Pediatrics. All circumcisions will be performed on the Yawkey 4 unit regardless.
- Consider deferring circumcision if the baby is escalating in NOWS symptoms until the infant is more stable.

**Discharge Planning:**

- Refer all opioid-exposed infants to the **SOFAR (Supporting Our Families Through Addiction and Recovery)** at BMC as a primary care option. Call 617-414-6672 to schedule an appointment with Dr. Costello, Dr. Stulac or the Green Team.
- Referral to **Baby Steps Program** for all infants with NOWS; give Baby Steps brochure
- **Early Intervention** referral for all infants with NOWS should be arranged through the ward assistant.
- **Ophthalmology** referral for all infants with NOWS due to higher risk of refractive errors: Call Rose Joseph at **4-4071** to schedule appointment with Dr. Christiansen at 4-6 months of age
- **Pediatric ID** follow-up appointment for Hepatitis C exposed infants
- If on **phenobarbital**, phenobarbital wean should be detailed in the discharge prescription and discharge summary
- Phone communication with primary care physician
- VNA for all infants with NOWS
- Document in the discharge summary if a **Plan of Safe Care** is in place based on Social Work assessment

**Contributing Departments:**

NOWS Working Group: Elisha Wachman, MD (NICU), Elizabeth Hutton, MD (Inpatient Pediatrics), Sue Minear, MD (Birth Place), Karan Barry, RN (Inpatient Pediatrics), Ginny Combs, RN (Birth Place), Donna Stickney, RN (NICU), Cheryl Slater, RN (Birth Place, NICU), Judy Burke, RN (NICU), Hannah Simons, RN (Birth Place), Julie Slomkowski, PharmD (Pharmacy), Kelley Saia, MD (Obstetrics)

**References:**

- 1) Hudak ML, Tan RC. Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics*, 2012; 129(2): e540-60. PMID:22291123; DOI: [10.1542/peds.2011-3212](https://doi.org/10.1542/peds.2011-3212)
- 2) Wachman EM, Newby PK, Vreeland J, et al. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence syndrome. *J Addict Med*, 2011; 5: 293-9. PMID: 21857233; DOI: [10.1097/ADM.0b013e3182266a3a](https://doi.org/10.1097/ADM.0b013e3182266a3a)
- 3) Jones HE, Heil SH, Tuten M, et al. Cigarette smoking in opioid-dependent pregnant women: neonatal and maternal outcomes. *Drug Alcohol Depend*, 2013; 131(3):271-7. PMID: 23279924; PMCID: [PMC3694998](https://pubmed.ncbi.nlm.nih.gov/PMC3694998/); DOI: [10.1016/j.drugalcdep.2012.11.019](https://doi.org/10.1016/j.drugalcdep.2012.11.019)
- 4) Wachman EM, Saia K, Humphreys R, et al. Revision of Breastfeeding Guidelines in the Setting of Maternal Opioid Use Disorder: One Institutions' Experience. *J Hum Lact*, 2016; 32(2): 382-7. PMID: 26514156; DOI: [10.1177/0890334415613823](https://doi.org/10.1177/0890334415613823)
- 5) Bagley SM, Wachman EM, Holland E, et al. Review of the assessment and management of neonatal abstinence syndrome. *Addict Sci Clin Pract*, 2014; 9(1): 19. PMID: 25199822; PMCID: [PMC4166410](https://pubmed.ncbi.nlm.nih.gov/PMC4166410/); DOI: [10.1186/1940-0640-9-19](https://doi.org/10.1186/1940-0640-9-19)
- 6) Jones HE, Seashore C, Johnson E, et al. Psychometric assessment of the Neonatal Abstinence Scoring System and the MOTHER NAS Scale. *Am J Addict*, 2016; 25(5): 370-3. PMID: 27287965; DOI: [10.1111/ajad.12388](https://doi.org/10.1111/ajad.12388)
- 7) Holmes AV, Atwood EC, Whalen B, et al., Rooming-In to Treat NAS: Improved Family-Centered Care at Lower Cost. *Pediatrics*, 2016; 137(6). PMID: 27194629; DOI: [10.1542/peds.2015-2929](https://doi.org/10.1542/peds.2015-2929)
- 8) Hall ES, Meinzen-Derr J, Wexelblatt SL. Cohort Analysis of a Pharmacokinetic-Modeled Methadone Weaning Optimization for Neonatal Abstinence Syndrome. *J Pediatr* 2015;167:1221-25.e1. PMID: 26477866; DOI: [10.1016/j.jpeds.2015.09.038](https://doi.org/10.1016/j.jpeds.2015.09.038)
- 9) Brown MS, Hayes MJ, Thornton LM. Methadone versus morphine for treatment of neonatal abstinence syndrome: a prospective randomized clinical trial. *J Perinatol*, 2015; 35(4): 278-83. PMID: 25357093; DOI: [10.1038/jp.2014.194](https://doi.org/10.1038/jp.2014.194)
- 10) Humbarger O, Galanto D, Saia K, Bagley SM, Wachman EM, et al. Childhood Health and Development in a Cohort of Infants Exposed Prenatally to Methadone or Buprenorphine. *J Addict Res Ther*, 2016; 7:263. <http://dx.doi.org/10.4172/2155-6105.1000263>
- 11) Howard MB, Schiff DM, Wachman EM, et al. [Impact of Paternal Presence at Infants' Bedside on NAS. \*Hosp Pediatr\*, 2017; Jan 30. Epub ahead of print.](https://doi.org/10.1093/peds/kwx001)
- 12) Oei HL, Melhuish E, Uebel H, et al. [NAS and High School Performance. \*Pediatrics\*, 2017, Jan 16. Epub ahead of print.](https://doi.org/10.1093/peds/kwx001)
- 13) Grossman M, Berkwitz A, Osborn R, Xu Y, Esserman D, Shapiro E, Bizzarro M, "An initiative to improve the quality of care of infants with neonatal abstinence syndrome" *Pediatrics*, June 2017.

# NOWS METHADONE ALGORITHM

*\*For preterm infants < 34 weeks, utilize NWAT scoring in place of ESC*

- Begin **ESC assessments** within **4 hours** of birth. Infants may be assessed on the mother skin-to-skin.
- Infants should be assessed every **3-4 hours** with routine feeds / cares.
- **NOWS Bundle of Care:** Encourage breastfeeding (if eligible), skin-to-skin with parents, parental

**1) Consider starting PRN Neonatal Methadone 1mg/ml oral solution 0.07mg/kg/dose q8 hours PRN after a team huddle if:**

- Infant with **any 1 “Yes”** responses to **ESC**: 1) **E = Poor feeding due to NOWS**, 2) **S = Sleep < 1 hour due to NOWS**, OR 3) **C = Console (Unable to Console within 10 minutes)** **AND:**
- **Non-pharmacologic care has been optimized first**, and non-NOWS causes ruled out
- Additional doses may be given **q8 hours PRN** for continued **“YES”** responses to **ESC** due to NOWS despite optimal non-pharm care. A **team huddle** and/or **MD notification** should occur around each **PRN** dose. Dosing may occur at **q6 hours** for severe cases with uncontrolled

**2) Further optimize non-pharmacologic care as **first-line treatment**:**

\* **CALM Cuddlers:** Call 44511 (Yawkey 5) or 45844 (Volunteer Services) to request a cuddler

\* **There are no maximum number of PRN methadone doses**

\* Infants who are not improving with PRN dosing should have a **huddle** to consider **standing Level 1**

**3) Level**      **Starting dose of STANDING Methadone 1mg/ml oral solution**

1	<b>0.2 mg/kg/day</b> PO divided q8 hours = 0.07 mg/kg/dose
2	<b>0.4 mg/kg/day</b> PO divided q8 hours = 0.13 mg/kg/dose
3	<b>0.6 mg/kg/day</b> PO divided q8 hours = 0.2 mg/kg/dose
4	<b>0.8 mg/kg/day</b> PO divided q8 hours = 0.27 mg/kg/dose

Always use **BIRTH WEIGHT** to dose methadone

**4) Increase oral methadone dose to next level if:**

- Continues to have **“Yes”** to **ESC due to NOWS**
- Methadone can be increased **1 time per day** (q16 hours)

**5a) Methadone Weaning:**

- Wean by **10%** of maximum dose in **mg/kg/day** once daily as tolerated if primarily **“NO”** for **ESC** over the past 24 hours.
- **Discontinue** methadone when dose is **10%** of maximum dose.
- **Consider increasing methadone interval** for infants with challenging weans in consultation with pharmacy
- Infants should be monitored for **48 hours** off methadone before discharge home.

**5b) Failed Weans:**

- If after a wean, persistent **ESC “Yes” due to NOWS**, then:
- Option 1: Consider **increasing methadone dose** by 10%.
  - Option 2: Attempt to **hold current dose** for up to 24 hrs, particularly towards the end of the weaning process.
  - Option 3: Consider **adding secondary agent** if <50% through wean.
  - Option 4: Towards end of the wean, may **increase interval** to q12 then q24 hours with pharmacy consultation

**6) Re-Initiation of methadone after discontinuation:**

- Consider for persistent **ESC “Yes” due to NOWS**
- Option 1: Can trial **PRN dosing** with **0.07mg/kg/dose**
- Option 2: Re-start at **20%** of maximum dose, then wean once down to **10% dose** before discontinuing.

**7) All methadone and buprenorphine** exposed infants

should be observed inpatient for a minimum of **5-7 days** for need for medication treatment.

\* Infants treated with **PRN methadone** must be monitored for **48 hours** after the final dose before discharge.

# NOWS Secondary Agent Algorithm

*\*For preterm infants < 34 weeks, utilize NWAT scoring in place of ESC*

## 1) Consider **adding secondary agent** if:

- the maximum oral methadone dose (level 4) is reached and symptoms persist with **ESC "Yes"** due to NOWS, OR if
- Stalled weaning for 2-3 days after first attempting methadone re-stabilization
- Use **Phenobarbital** as secondary agent particularly if infant is polypharmacy, benzodiazepine, illicit drug (including heroin) and/or alcohol exposed or if infant exhibiting severe neurological symptoms.
- Use **Clonidine** as a third-line agent if infant has not responded well to Phenobarbital

**2a) Phenobarbital** loading dose = 20 mg/kg PO

Always use **BIRTH WEIGHT** to dose phenobarbital

## 3a) Reload **phenobarbital** if:

- Persistent **ESC "Yes"** due to NOWS
- **10mg/kg/dose PO every 8-12 hours as needed x 2 more doses** until the cumulative total of all loading doses reaches a maximum of 40mg/kg

**2b) Clonidine** dose = 1 mcg/kg PO q4 hours

- Monitor blood pressure every 4 hours. Hold dose if SBP <65 or DBP <35.
- Never increase dose > 1 mcg/kg/dose

**3b) Once stable, wean off methadone, then decrease **clonidine** dose every 24 hours as tolerated by extending the dosing interval from q4hr to q8hr to q12hr, then off.**

- After discontinuation, observe for 48 hrs minimum before preparing for discharge.

**4a) Begin **phenobarbital** maintenance dosing** 24 hours after last loading dose and give maintenance dose every 24 hours. Maintenance dose depends on sum of all loading doses received:

### Cumulative Sum of Loading Doses

20 mg/kg  
30 mg/kg or higher

### Maintenance Dose

5mg/kg/day  
6.5mg/kg/day

## **Phenobarbital** serum levels:

- If a cumulative total of 30mg/kg of loading doses have been given, **draw a serum level** prior to giving any further loading doses.
- For all infants on Phenobarbital, obtain a baseline trough level 48 hours following the last loading dose.
- Ideal phenobarbital serum level to control NOWS is 20-30mg/ml. If the level is >40mg/ml, consider decreasing the dose and contact the pediatric pharmacist for additional guidance.
- Additional serum levels may be drawn as clinically indicated.

**5a) Once an infant is off of oral methadone, **phenobarbital** may be **weaned** by the inpatient team or the primary care physician.**

- Phenobarbital can generally be discontinued after a 4-8 week taper
- Wean phenobarbital by 20% every week, as long as the infant is not exhibiting withdrawal symptoms
- Include phenobarbital weaning in **discharge Rx** and instructions in the **discharge summary**

## **Appendix A – IV Morphine Sulfate Dosing for NPO Patients with NOWS**

- Note that IV morphine is not well studied for use for NOWS and may put the patient at greater risk for adverse effects such as respiratory depression and sedation.
- **Indications for us of IV morphine for NOWS:** Infants unable to tolerate enteral methadone dosing
- **Assessments:** Preterm infants < 34 weeks GA should be assessed with the **NWAT** (see NICU Sedation Guidelines) instead of ESC every 3-4 hours with cares. Infants should be started on IV morphine for **NWAT scores >3 on 2-3 consecutive assessments**.
- **Consultation:** If starting a baby on IV morphine protocol, please notify the pediatric pharmacist within 24 hours of initiation for assistance with management.
- **Initiating IV Morphine Infusion:**
  - o IV morphine should be ordered as a **continuous morphine infusion** through the **NICU NAS/NOWS order set**.
  - o **Initial dose: 0.01 – 0.02mg/kg/hour.** Dosing should be based on **birth weight**.
  - o **Concentration:** Please reference the **NICU Continuous Infusion Binder** for drip rates to select the most appropriate concentration. Most patients will require the **0.05mg/mL** concentration. Other options include the 0.1mg/mL or 0.5mg/mL solutions. **Drip rates should be rounded to the nearest “0.1mL/hr” for pump accuracy.**
  - o **Carrier fluid:** Select D5, D10, or NS
- **Escalation of IV Morphine Infusion:**
  - o If infant has continued “NWAT scores >3, the morphine infusion should be increased in increments of **0.01mg/kg/hr** q12-24 hours to a maximum recommended dose of **0.05mg/kg/hr**.
  - o If NWAT scores consistently >3 on maximum dosing of IV morphine, second-line therapy with **IV phenobarbital** may be considered at this time. Dosing is equivalent to PO phenobarbital per **NOWS Secondary Agent Algorithm**.
- **Weaning of IV Morphine Infusion:**
  - o Once infant has stable NWAT scores  $\leq 3$  for 24 hours, may wean the IV morphine by **0.01mg/kg/hr** daily.
- **Conversion to PO Methadone:**
  - o Once able to tolerate enteral medications and the infant has weaned down to a maximum of **0.03mg/kg/hr** of the IV morphine solution, the IV morphine can be converted to PO methadone solution at a ratio of **2mg IV morphine = 1mg PO methadone**.
  - o Should then proceed to **wean by 10%** of the **maximum PO daily dose** until down to **20% of maximum**, then discontinue.

### **Sample Calculation for Conversion from IV morphine infusion to PO methadone:**

Morphine IV infusion = 0.01mg/kg/hr

Total daily dose of IV morphine = 0.01mg/kg/hr  $\times$  24 hours = 0.24mg/kg/day

2:1 conversion to total daily dose of PO methadone = 0.24mg/kg/day divided by 2 =

0.12mg/kg/day