

# Neonatal Abstinence Syndrome

Grace Chai, PharmD

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## Neonatal Abstinence Syndrome

- **Introduction**
  - NAS is often found in infants withdrawing from substances they have come physically addicted to in utero
  - Neonates in the NICU often present with similar physical signs and symptoms when a narcotic or benzodiazepam is abruptly discontinued after prolonged periods of time on a narcotic or benzodiazepam drip
  - The Neonatal Abstinence Syndrome Guideline has been developed to standardize the prevention and treatment of iatrogenic abstinence syndrome in NICU patients

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## Definitions

- **Addiction:** complex pattern of behaviors characterized by the repetitive, compulsive use of a substance, need to obtain drug, and high incidence of relapse after treatment
- **Iatrogenic:** syndrome inadvertently induced by medical treatment
- **Physical dependence:** neuroadaptation that necessitates continued administration of the drug to maintain physiologic equilibrium and prevent withdrawal syndrome
- **Psychological dependence:** need to continue a substance for its euphoric effects
- **Tolerance:** decrease in drug's effects over time resulting in need for higher doses to provide adequate response
- **Withdrawal:** physical signs and symptoms that occur with the abrupt discontinuation of a narcotic or sedative agent

Tobias, Joseph D. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Critical Care Medicine*, 2000, 28(6): 2122-2132

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## Mechanism of Tolerance and Physical Dependence



- **Opioids: opioid-receptor binding** → conformational change in receptor resulting in:
  - Interaction with G protein system
  - Inhibition of cAMP production
  - Hyperpolarization of neural pathways involved in nociception
  - Decreased release of excitatory neurotransmitters
- **Chronic opioid exposure** → uncoupling of opioid receptors from G proteins → normalization of cAMP
- **Abrupt opioid withdrawal** → greater ↑ cAMP leading to:
  - ↑ afferent CNS activity
  - Stimulation of reticular activating system and sympathetic centers
  - ↑ autonomic activity (i.e. tachycardia and hypertension)



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## Mechanism of Tolerance and Physical Dependence



- **Tolerance and physical dependence occurs with all opioids with repeated and chronic administration**
  - Related to the occupancy of the receptor by an agonist and the specificity or degree of binding of the agonist at the receptor
  - Occurs more often in:
    - continuous >> intermittent administration
  - Tolerance develops more rapidly with:
    - Synthetic opioids (fentanyl) >> nonsynthetics (morphine)
  - Some level of tolerance can develop within a few hours of opioid administration and some cross-tolerance can occur between all opioid agonists
- **No ceiling dose of opioid**
  - With chronic use, opioids must be titrated to analgesic response

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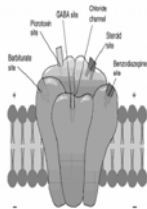
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## Benzodiazepines (BDZ)



- **BDZ increase affinity of GABA for cell surface receptors** located on postsynaptic neurons → ↑ chloride conductance and hyperpolarization
- **Chronic BDZ exposure** → downregulation or ↓ sensitivity of GABA receptors → ↓ chloride conductance and ↓ hyperpolarization
- **Abrupt BDZ withdrawal** → ↓ pharmacological efficacy of the same concentration of GABA → disinhibition of the CNS
- **Tolerance and physical dependence occur with all BDZ with repeated and chronic administration**



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## Methadone and Lorazepam



- **Methadone**
  - Synthetic opioid with level of analgesia and sedation similar to morphine
  - Agonist at both  $\mu_1$ ,  $\mu_2$  and kappa opioid receptors
- **Lorazepam**
  - Benzodiazepine
- **Both agents are have IV and PO formulations with relatively high oral bioavailabilities and long elimination half life**
  - Methadone  $T_{1/2} = \sim 19$  (4-62 hours)
  - Lorazepam  $T_{1/2} = \sim 40$  (18-73 hours)

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## Neonatal Abstinence Syndrome



- **Risk and severity NAS depends on dose and duration of opioid and/or BDZ used**
- **Onset of withdrawal signs and symptoms depend on the half-life of the drug. Delayed clearance (impaired liver/renal function) will delay onset**
- **NAS Score (modified Finnegan) will allow standardization of reporting and objectify subjective data**
  - 0-7 mild; 8-11 moderate; 12-15 severe
  - No neonatal withdrawal scoring tool has been validated

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## NAS Signs and Symptoms



Central Nervous System	Gastrointestinal	Vasomotor / Other
Cry—excessive or high-pitched	Excessive sucking	Sweating
Sleep difficulty	Poor feeding	Fever – low grade
Skin breakdown (excoriation)	Vomiting	Nasal Stuffiness
Hypertonia / hyperreflexia	Diarrhea	Respiratory distress
Myoclonic jerks	Frequent sneezing	Nasal Flaring
Seizures	Frequent yawning	

- **In the pediatric population:**
  - Unique signs of narcotic withdrawal: upper airway obstruction, irregular involuntary muscle activity
  - Unique signs of benzodiazepine withdrawal: increased anxiety, fear, extreme agitation, and refractory seizures

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## Prevention and Treatment of NAS



- Careful tapering of opioid and BDZ infusions is the first step in prevention
- Begin weaning protocol once patient's illness has stabilized
- In high risk patients (high dose and/or long treatment period) it is appropriate to began prophylactic methadone and/or lorazepam in anticipation of NAS
- NAS may not apply to some patients in the NICU, consider using the critical care algorithm and WAT (withdrawal assessment tool) in older, full term patients

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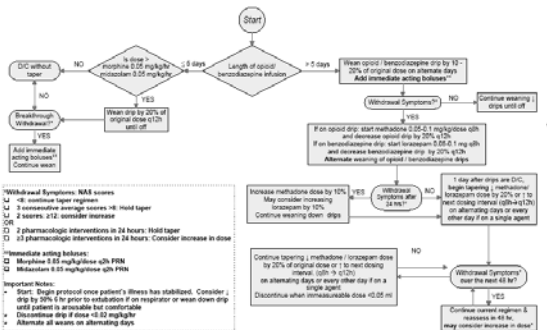
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### NEONATAL ABSTINENCE SYNDROME PREVENTION AND TREATMENT



**Withdrawal Symptoms: NAS scores**

- 1-4 0-8 cumulative taper regimen
- 5-7 3 consecutive average scores  $\geq 4$  hold taper
- 8-10 4 scores  $\geq 10$  consider increase
- 11-12 2 pharmacologic interventions in 24 hours: Hold taper
- 13-15 3 pharmacologic interventions in 24 hours: Consider increase in dose

**Intermediate acting boluses:**

- 1 Methadone 0.05 mg/kg/dose q12h PRN
- 2 Lorazepam 0.05 mg/kg/dose q12h PRN

**Important Notes:**

- Start: Begin protocol once patient's illness has stabilized. Consider 2 drip to 10% if prior to evaluation if on respirator or wean down drip until patient is available but comfortable
- Discontinue drip if dose  $< 0.05$  mg/kg/hr
- Alternate all weans on alternating days

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## Prevention and Treatment of NAS



- If on morphine/midazolam  $\leq 5$  days:
  - Begin NAS scoring tool when drip is discontinued for at least 48 hours if withdrawal is suspected
  - Premature infants may have lower risk for NAS possibly due to CNS immaturity
    - If low dose (morphine  $< 0.05$  mg/kg/hr, midazolam  $0.05$  mg/kg/hr), consider D/C without taper
    - If dose is higher, may alternate weaning drip(s) by 20% of original dose
    - Add on PRN boluses of morphine  $0.05$  mg/kg/dose and midazolam  $0.05$  mg/kg/dose q2-4hr PRN for signs and symptoms of breakthrough withdrawal

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## Prevention and Treatment of NAS



- **If on morphine/midazolam > 5 days:**
  - Wean morphine and/or midazolam drip ↓ by 20% of original dose on alternating days, may wean by 10% of original dose on **alternating days** for high risk/sensitive patients
  - Add rescue boluses: morphine and/or midazolam 0.05 mg/kg/dose q2-4h PRN
  - When extubating, consider ↓ drip by 50% or ↓ drip until patient is arousable but comfortable at 6 hours prior to extubation if on respirator
  - BEGIN SCORING TOOL
  - Once morphine and/or midazolam drip is < 0.1 mg/kg/hr, add on methadone and/or lorazepam at 0.05-0.1 mg/kg/dose q8h to be administered on an **alternating schedule**
  - Once oral agents have been started, alternate decreasing of opioid/benzodiazepine drip by 20% of original dose q12h until drips are off

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## Prevention and Treatment of NAS



- **If NAS scores <8: patient is not experiencing significant withdrawal, continue taper schedule**
- **If 3 consecutive average NAS scores of 8-12 OR 2 rescue boluses: Hold taper**
- **If 2 NAS scores of ≥ 12 or ≥ 3 rescue boluses: increase dose of methadone/lorazepam; continue wean of drips until off**
- **Repeat cycle as needed**

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### Neonatal Withdrawal Assessment

Patient Initial: \_\_\_\_\_

Date: \_\_\_\_\_ Date of discontinuation of continuous infusion: \_\_\_\_\_

Score patient for minimum of 48 hours after discontinuation of infusion.

Scores 0-6: Moderate severity 8 hours

Scores 0-2: Severe 16-24 hours every 2 hours

System	Signs & Symptoms	Neonatal Abstinence Score (NAS)			
		0	1	2	3
CNS	Hyporeactivity	0	1	2	3
	Comatose/STP	0	1	2	3
	Stimex <2 hr after feed	0	1	2	3
	Stimex <2 hr after feed	0	1	2	3
	Crying during sleep	0	1	2	3
	Very slow return Moro reflex	0	1	2	3
	Mild tremors/drooping	0	1	2	3
	Mild tremors/tremors (shakiness)	0	1	2	3
	Mild tremors/parosmia/parosmia	0	1	2	3
	Exaggerated/parosmia/parosmia	0	1	2	3
GI	Emesis/vomiting	0	1	2	3
	Feeding intolerance	0	1	2	3
	Prone to vomiting	0	1	2	3
	Colic/flatulence	0	1	2	3
	Wetness/lethargy	0	1	2	3
Vital	Respiratory	0	1	2	3
	Power SP 3 to 36 SPC	0	1	2	3
	AP 30 to 36 SPC	0	1	2	3
	Respiratory (CPR in 15 hrs)	0	1	2	3
	Apnea	0	1	2	3
	Heart rate	0	1	2	3
	Temperature (C/98.6 in 15 hrs)	0	1	2	3
	Weight gain	0	1	2	3
	Fluid intake	0	1	2	3
	Stool volume & consistency	0	1	2	3
Urine output	0	1	2	3	

Adapted from "The Neonatal Abstinence Scale"

0-6: Moderate severity 8 hours

0-2: Severe 16-24 hours every 2 hours

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## Prevention and Treatment of NAS



- When patient is stabilized on wean: begin taper down of methadone/lorazepam by 20% of original dose or increase interval (q8h → q12h) on alternating days or every other day if on a single agent
- Continue to assess with scoring tool until patient is on stable taper to discontinue
- Please consult NICU pharmacist for written weaning schedule or assistance as needed

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