Neonatal Abstinence Syndrome

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Disclosures

I have no financial disclosures

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Objectives

- Identify the substances associated with neonatal abstinence syndrome (NAS)
- Discuss the pathophysiology of NAS
- Understand the symptoms/clinical manifestations of NAS
- Discuss the evaluation of NAS via scoring systems
- Understand the treatment options available and which patients qualify for treatment
  - Understand criteria for escalation/weaning of pharmacologic therapies
- Discuss discharge criteria, follow-up needs, and outcomes of NAS

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What is Neonatal Abstinence Syndrome?

"Neonatal abstinence syndrome (NAS) is a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy"

- Chronic fetal exposure to substances
- Multisystem disorder – primarily affects CNS, autonomic nervous system, and GI tract
- NAS is rarely fatal, but may cause significant illness/symptoms and can result in prolonged hospital stays

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Substances Associated with NAS

- Alcohol
- Antidepressants – SSRIs, SNRIs, TCAs
- Barbiturates
- Benzodiazepines
- Caffeine
- Inhalants
- Marijuana
- Opiates
- Tobacco/nicotine
- Stimulants – cocaine, methamphetamines

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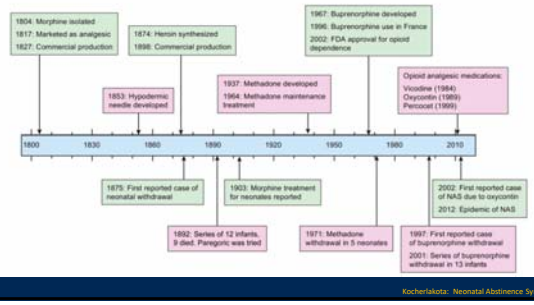
A Look to the Past – History of NAS



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Kocherlakota: Neonatal Abstinence Syndrome

A Look to the Past – History of NAS

- Opium use dates back to ancient civilizations
- Opium addiction first recorded at end of 18th century
- Congenital morphinism (opiate withdrawal following birth) first diagnosed in 1875
  - Most of the infants with this diagnosis died
  - 1903 – first case of infant surviving after treatment with morphine
  - 1947 – first successful treatment of secondary seizures
- Subsequently renamed Neonatal Abstinence Syndrome

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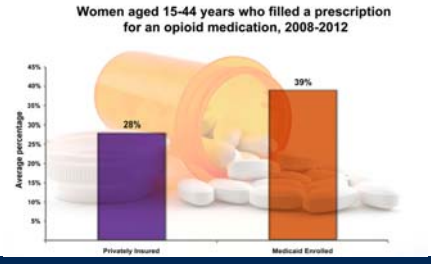
Opiate Use in Reproductive Age Women



CDC 2015

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Epidemiology

Maternal opioid use is increasing

- Increased from 1.2 to 5.6 mothers per 1000 live births from 2000-2009
- 6% of mothers used opioids for more than a month during pregnancy
- Rise in methadone maintenance treatment accounts, in part, for increased incidence of NAS

The incidence of NAS has been increasing in the US

- Incidence of NAS increased from 1.2 to 5.8 per 1000 hospital births per year from 2000-2012

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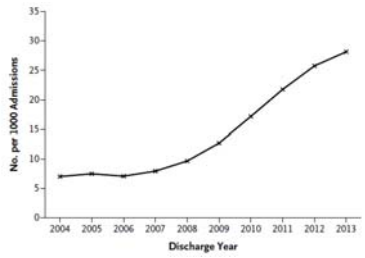
NICU Admissions for NAS



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Tolia: Increasing incidence of the NAS in U.S. NICUs

Evolution of NAS

- Prior to 1970, NAS generally secondary to morphine or heroin use
- Today NAS may be secondary to use of morphine, heroin, methadone, buprenorphine, prescription opiates, antidepressants, anxiolytics, and other substances
- NAS has become more complex and severe
  - Increased use of opiates
  - Complicated by simultaneous use of multiple substances (including illicit drugs)

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Opioid Receptors

Receptor	Location	Function
Mu (μ)	Brain, spinal cord, peripheral sensory neurons, intestinal tract	Analgesia, physical dependence, respiratory depression, euphoria, reduced GI motility, physical dependence
Kappa (κ)	Brain, spinal cord, peripheral sensory neurons	Analgesia, anti-convulsant effects, hallucinogenic effects, diuresis, dysphoria, sedation
Delta (δ)	Brain, peripheral sensory neurons	Analgesia, antidepressant effects, convulsant effects, physical dependence

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Pathophysiology

- Pathophysiology poorly understood
- Many factors affect the accumulation of opioids in the fetus.
  - Opiates have low molecular weights, are water soluble and lipophilic thus they are easily transferred to the fetus from the placenta
    - This process increases with increasing gestational age
  - Synthetic opiates cross the placenta more readily than semi-synthetic opiates
  - Combination of cocaine or heroin with methadone increases permeability of methadone across the placenta
  - Drugs can readily cross the blood brain barrier of the fetus
  - Prolonged half life common in the fetus

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Pathophysiology

Opiate withdrawal is a complex phenomenon
- Cellular and molecular mechanism is poorly understood, even in adults
- More complicated in neonates given immature neurologic development

Locus Coeruleus of the Pons is the most important center of activity in opioid withdrawal
- Lack of opiates causes increased production of norepinephrine – which is responsible for most of the signs of NAS

No relationship between maternal opioid dose and NAS

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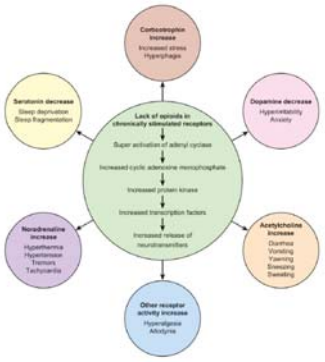

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Pathophysiology

- SSRIs/SNRIs cause withdrawal symptoms due to excess serotonin and norepinephrine
- TCA's cause a cholinergic rebound
- Benzodiazepine withdrawal probably cause increased GABA release
- Methamphetamine withdrawal may be secondary to decrease in dopamine and serotonin
- Inhalant withdrawal involves dopamine, glutamate, and GABA pathways

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Risk Factors for Development/Severity of NAS

TABLE 2 Risk Factors for Increasing Severity and/or Intensity of NAS

Definite	Probable
Term[97,98,108]	Male gender[112,113]
Good birth weight[97,109]	Methadone[43,46]
Polydrug abuse[100,107, 110]	Smoking[97,109,114]
Combination with benzodiazepines[97,111]	Combination with SSRIs[97,109,115]
μ-opioid receptor (OPRM1 118 AA) positive[105]	
Catechol-O-methyltransferase (COMT 158 AA) positive[105]	

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Kocherlakota: Neonatal Abstinence Syndrome

Symptoms/Clinical Manifestations

Dysfunction in 4 domains (state control and attention, motor and tone control, sensory integration, and autonomic functioning) cause the characteristic signs of NAS

- High pitched cry/irritability
- Sleep/wake disturbances
- Alterations in tone or movement (hyperactive primitive reflexes, hypertonicity, and tremors)
- Feeding difficulties
- GI disturbances (vomiting and loose stools)
- Autonomic dysfunction (sweating, sneezing, mottling, fever, nasal stuffiness, and yawning)
- Failure to thrive (may require more than 150kcal/kg/day)

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Clinical Manifestations

- Seizures reported in 2-11% of infants with NAS
  - May be caused by different drugs, including opiates, barbiturates, alcohol, and sedative-hypnotics
  - Cause of seizures unknown, abnormal EEG changes can be seen in >30% of neonates withdrawing from opiates
  - Naloxone use must be avoided in cases of chronic maternal opioid use as it can precipitate seizures
- SGA (birth weight less than 10th percentile)
- Respiratory complications (tachypnea and apnea)

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Prematurity and NAS

Incidence and severity of NAS less extensive in preterm neonates

- Decreased cumulative exposure
- Decreased transmission across placenta in earlier gestations
- Decreased drug clearance
- Decreased excretion due to renal and hepatic maturity
- Decreased receptor development and sensitivity

Assessment of symptoms can be difficult as scoring systems are not intended for premature neonates

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Timing of Withdrawal

- Signs may be present at birth and not reach peak until 3-4 days of life
- May not appear until 10-14 days of life
- Subacute withdrawal may persist for 4-6 months
- Neurologic irritability (abnormal Moro reflex) noted to last up to 7-8 months of age

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Timing of Withdrawal

TABLE 1 Onset, Duration, and Frequency of NAS Caused by Various Substances

Drug	Onset, h	Frequency, %	Duration, d
Opioids			
Heroin	24–48	40–80[27]	8–10
Methadone	48–72	13–84[37]	Up to 30 or more
Buprenorphine	36–60	22–67[48,49]	Up to 28 or more
Prescription opioid medications	36–72	5–20[96,60]	10–30
Nonopioids			
SSRIs	24–48	20–30[64]	2–6
TCAs	24–48	20–50[64]	2–6
Methamphetamines	24	2–49[101]	7–10
Inhalants	24–48	48[70]	2–7

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Kocherlakota: Neonatal Abstinence Syndrome

Timing of Withdrawal

TABLE 2 Maternal Nonnarcotic Drugs That Cause Neonatal Psychomotor Behavior Consistent With Withdrawal

Drug	Signs	Onset of Signs	Duration of Signs*	Ref. No.
Alcohol	Hyperactivity, crying, irritability, poor suck, tremors, seizures; onset of signs at birth, poor sleeping pattern, hyperphagia, diaphoresis	5–12 h	18 mo	14,15
Barbiturates	Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, disturbed sleep; onset first 24 h of life or as late as 10–14 d of age	1–14 d	4-6 mo with prescription	12,13
Caffeine	Jitteriness, vomiting, bradycardia, tachypnea	At birth	1-7 d	161
Chlordiazepoxide	Irritability, tremors; signs may start at 21 d	Days–weeks	9 mo; 11/2 mo with prescription	11
Clomipramine	Hypothermia, cyanosis, tremors; onset 12 h of age		4 d with prescription	162
Diazepam	Hypotonia, poor suck, hypothermia, apnea, hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, tachypnea (mother receiving multiple drug therapy)	Hours–weeks	8 mo, 10–66 d with prescription	10
Ethchlorvynol	Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia (mother receiving multiple drug therapy)		Possibly 10 d with prescription	163
Glutethimide	Increased tone, tremors, opisthotonos, high-pitched cry, hyperactivity, irritability, colic		6 mo	164
Hydroxyzine	Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, increased respiratory and heart rates, feeding problems, clonic movements (mother receiving multiple drug therapy)		5 wk with prescription	58
Meprobamate	Irritability, tremors, poor sleep patterns, abdominal pain		9 mo, 3 mo with prescription	165
SSRIs	Crying, irritability, tremors, poor suck, feeding difficulty, hypertonia, tachypnea, sleep disturbance, hypoglycemia, seizures	Hours–days	1–4 wk	31–33,35

* Prescription indicates the infant was treated with pharmacologic agents, and the natural course of the signs may have been shortened.

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Clinical Report: Neonatal Drug Withdrawal 2012

Laboratory Testing

- NAS is a clinical diagnosis, but toxicological confirmation is necessary to identify the substance(s) mother was using or abusing
- Urine testing has low sensitivity and high false negative rate – only infants with recent exposure will have a positive test
- Meconium analysis is sensitive and specific
  - Drugs excreted into either hepatobiliary system or amniotic fluid via renal excretion
  - Reflects drug exposure in second and third trimesters
  - Testing often performed offsite and results may take days to weeks
  - Meconium passage may be delayed, may have already occurred in utero, and must be collected before contaminated with transitional stools
  - Meconium is light and temperature sensitive so proper storage is important

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Laboratory Testing

- Umbilical cord testing using immunoassays is a promising method of testing, but currently the utility in medical management is limited
- Testing of neonatal hair is challenging and often culturally unacceptable so medical management is limited
- A combination of maternal urine and neonatal meconium usually yields the best results
- Need for consent for testing varies among states
- Each hospital should adopt a policy for maternal and newborn screening that complies with laws and avoids discriminatory practices

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TABLE 3 Urinary Screening for Various Drugs and Approximate Duration of Detection in the Neonate[14,119–122]

Substance	Compound/Metabolite/Usage	Duration of Detectability
Alcohol[120]	Ethanol	Few h
	Fatty acid ethyl esters	Up to 5 d
	Ethyl glucuronide	Up to 30 h
	Ethyl sulfate	
Amphetamines	Amphetamine	1–2 d
	Methamphetamine	1–2 d
Barbiturate	Short acting	<2 d
	Long acting	1–7 d
Benzodiazepines	Short acting	1–7 d
	Long acting	Up to 30 d
Cocaine	Cocaine	6–8 h
	Metabolites	2–5 d (up to 10–22 d with heavy use)
Marijuana	Single use	1–3 d
	Moderate use	5–7 d
	Heavy	up to 10 d
	Chronic heavy use	up to 30 d
Opiates	Heroin, morphine, codeine	1–2 d
	Hydromorphone, oxycodone	2–4 d
	Methadone	2–3 d
	Methadone metabolite	Up to 8 d
	Buprenorphine[120]	2–3 d
	Buprenorphine	2–3 d
	Norbuprenorphine	
Phencyclidine		1 to 8 d

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Comorbidities

- Sexually transmitted infections
  - Syphilis
  - Chlamydia and gonorrhea
  - Hepatitis C
  - HIV
- Maternal polydrug use
- Psychiatric comorbidity common in substance abusing women

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NAS Scoring

- Several scoring systems have been developed and verified to evaluate withdrawal symptoms
  - Finnegan NAS scoring system
  - Lipsitz tool
- All scoring systems are subject to interobserver variability
- Tools measure the severity of symptoms and are used to initiate, escalate, and wean pharmacologic therapies
- In each birth center caring for infants with NAS, a scoring system should be adopted
- Management protocols should be developed using the scoring systems
  - Decreases duration of opioid exposure and length of stay

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NAS Scoring

- Finnegan Scoring system and its modified versions are designed for term neonates
- It is the most widely used scoring method
- Major limitation is non-applicability to <37 weeks GA, and babies older than 30 days
- NAS scoring should begin at birth and ongoing assessments should be performed every 3-4 hours (after feeds) during hospital stay
- Score should represent status of infant at the time of feeds and in the preceding interval

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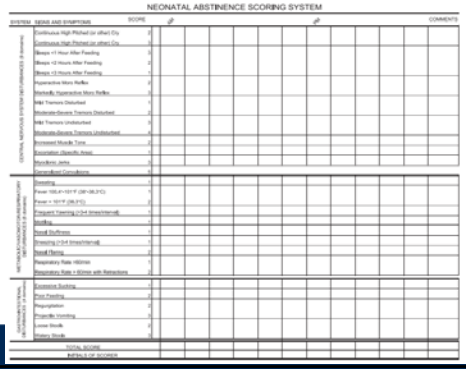
NEONATAL ABSTINENCE SCORING SYSTEM

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Finnegan Scoring System

CNS Disturbance

- Excessive high pitched cry (2)
- Continuous high pitched cry (3)
- Sleeps <1 hr after feeding (3)
- Sleeps <2 hrs after feeding (2)
- Sleeps <3 hes after feeding (1)
- Hyperactive Moro Reflex (2)
- Markedly Hyperactive Moro reflex(3)
- Mild tremors: Disturbed (1)
- Mod-Severe tremors: Disturbed (2)
- Mild tremors: Undisturbed (3)
- Mod-Severe tremors: Undisturbed (4)
- Increased Muscle tone (2)
- Excoriation (specific areas) (1)
- Myoclonic Jerks (3)
- Generalized Convulsions (5)

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Finnegan Scoring System

Metabolic/Vasomotor/Respiratory Disturbances

- Sweating (1)
- Fever 100.4-101°F/38-38.3°C (1)
- Fever >101°F/38.3°C (2)
- Frequent Yawning [>3-4x/interval] (1)
- Mottling (1)
- Nasal Stuffiness (1)
- Sneezing [>3-4x/interval] (1)
- Nasal Flaring (2)
- Respiratory Rate >60/min (1)
- Respiratory rate >60/min with retractions (2)

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Finnegan Scoring System

GI Disturbance

- Excessive sucking (1)
- Poor feeding (2)
- Regurgitation (2)
- Projectile vomiting (3)
- Loose Stools (2)
- Watery Stools (3)

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Supportive Care

- Should be performed in ALL neonates, may help to avoid pharmacologic treatment, and lead to earlier discharge
- Decrease stimuli – quiet, dark environment
- Avoid overheating
- Gentle handling
- Swaddling
- Encourage skin to skin contact
- Feed on demand
- Consider need for higher caloric density formula/fortified breast milk to supplement increased caloric needs
- Rooming in with mother and baby also decreases the severity of withdrawal

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Breastfeeding

- Multiple studies have shown that breast milk contains only minimal quantities of methadone and buprenorphine
  - The amount of methadone or buprenorphine in breast milk is too small to treat NAS
- Sudden discontinuation of breast milk is not associated with the worsening of NAS
  - However, gradual weaning from breastfeeding is advised
- Breastfeeding increases mother-infant bonding, enhances maternal confidence, and encourages active maternal participation in the management of the infant
- Breastfeeding may decrease the incidence of NAS, the need for pharmacological treatment, and the length of the hospital stay
- Breastfeeding is contraindicated only if the mother is taking illicit drugs, has polydrug abuse, or is infected with HIV

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Pharmacologic Treatment

- Required in 27-91% of neonates with NAS
- Aimed to improve short-term clinical symptoms
- Given complex nature of withdrawal and unknown effects of various drugs, currently data is limited regarding optimal pharmacologic agents for treatment of NAS
  - Opioid therapy is the preferred treatment based on current literature and AAP recommendations
- Medications required when:
  - Supportive therapy fails to control the signs and symptom
  - NAS scores remain high
  - Serious signs are observed, such as seizures
  - Withdrawal is associated with severe dehydration because of diarrhea and/or vomiting
- Initiate pharmacologic therapy using 24 rule for NAS scoring
  - 3 consecutive scores $\geq$ 8 **OR** 2 consecutive scores $\geq$ 12

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Pharmacologic Treatment

- Delays in administration of pharmacological therapy are associated with higher morbidity and longer hospital stays
- The AAP clinical report from 2012 recommends that either morphine or methadone are the preferred opioids for treating NAS
- Buprenorphine is a new option for the treatment
  - Given sublingually
  - No large-scale studies are available to support its use
- Paregoric is NOT recommended because it contains multiple opiates and alcohol
- Tincture of opium has 25 times higher concentration of morphine than oral morphine solutions which increases likelihood of overdose
- Sedatives, such as diazepam and chlorpromazine, are not useful due to their prolonged half-lives and associated complications

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Pharmacologic Treatment

Morphine

- Most commonly preferred medication
- Decreases incidence of seizures
- Prolongs length of hospital stay
- Short half-life requiring q3-4 hour dosing intervals
- Dose can be escalated rapidly for higher scores
- Weaning must be gradual

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Pharmacologic Treatment

Methadone

- Alternative to morphine treatment
- Used more commonly in US than in other countries
- Administered twice per day
- Long half-life
- Difficult to titrate methadone dose

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Pharmacologic Treatment

Second medication may be required if the infant's symptoms are not adequately controlled by a single medication therapy

- Clonidine and phenobarbital are common adjunctive agents

Clonidine

- Often is the preferred second line medication
- Shown to be effective as an adjunctive medication to opioid therapy for the treatment of NAS
- Theoretical risk of hypotension and bradycardia may always prohibit increasing its dose

Phenobarbital

- A systematic review compared phenobarbital with supportive care alone and showed that phenobarbital did not reduce treatment failure or the time required to regain birth weight
- Does not prevent seizures at the dosage administered for withdrawal
- Used as an adjuvant, especially in infants suffering withdrawal from polydrug abuse
- Disadvantages: sedating, may be difficult to wean

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Pharmacologic Treatment and Dosing

TABLE 4 Pharmacological Treatment Options for NAS

Medication	Mechanism of Action	Dose	Advantages	Disadvantages
Morphine	Natural μ-receptor agonist	0.05–0.2 mg/kg/dose q 3–4 h Increase by 0.05 mg/kg Maximum dose: 1.3 mg/kg/day[141]	No alcohol Short half-life (9 h)	Sedation Apnea Constipation Frequent dosing
Methadone	Synthetic complete μ-receptor agonist N-methyl-d-aspartate antagonist	0.05–0.1 mg/kg/dose q 12 h, increase by 0.05 mg/kg q 48 h Maximum dose: 1 mg/kg/d[27]	Long half-life (26 h) 12 hourly doses	Longer duration of treatment Alcohol 8% Frequent follow-up needed (Variable half-life)
Phenobarbital	γ-amino butyric acid agonist	Loading dose: 16 mg/kg Maintenance dose: 1–4 mg/kg/dose q 12 h[130]	Long half-life (45–100 h) Monitor level	Possible hyperactivity High treatment failure Alcohol 15% Drug-drug interactions Sedation
Clonidine	α-adrenergic receptor agonist	Initial dose: 0.5–1 μg/kg, followed by 0.5–1.25 μg/kg per dose q 4–6 h[54]	Nonnarcotic antagonist No sedation No alcohol Long half-life (44–72 h) Monitor level	Hypotension Abrupt discontinuation may cause rapid rise of blood pressure and heart rate
Buprenorphine	Semi-synthetic partial μ-receptor agonist, κ-receptor antagonist	Dose: 4–6 μg/kg/dose q 8 h Maximum dose: 60 μg/kg/d[130]	Sublingual route Half-life (12 h)	Alcohol 30% Adjuvant medications required

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Medication Use in Infants with NAS

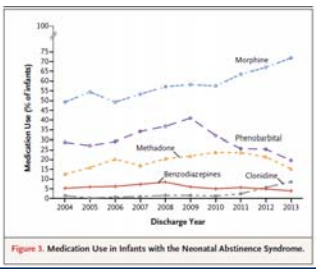

Figure 3. Medication Use in Infants with the Neonatal Abstinence Syndrome.

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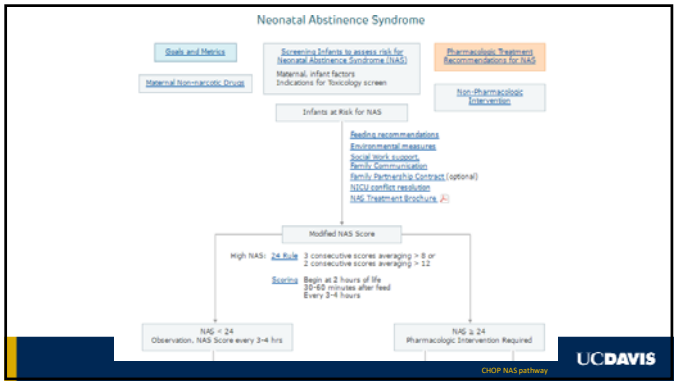
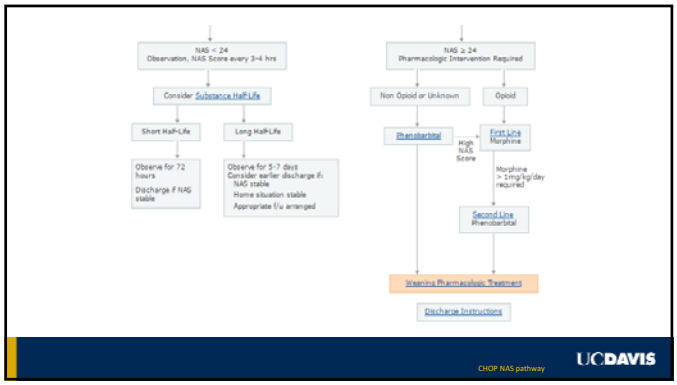
Tolia: Increasing Incidence of the NAS in U.S. NICUs





Escalating Therapy

- Allow infant to stabilize 12-24 hours after starting initial dose
- Increase dose by 10-20% (of original dose) for combined scores of ≥24 on 2-3 consecutive scores
- Dose may be increased as needed every 12 hours until symptoms are controlled
- Consider adding phenobarbital if:
  - Polysubstance exposure, prominent CNS findings (tremors, increased muscle tone), AND morphine dose exceeding 1 mg/kg/day with NAS scores remaining ≥24 OR unable to wean for 2 consecutive days
- Consider adding clonidine if:
  - NAS score primarily elevated secondary to autonomic over stiulation (sweating, mottling, sneezing, fevers, etc), AND morphine dose exceeding 0.1mg/kg/dose Q3 hours and still not stabilized

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Stabilization and Weaning Therapy

- Once stabilized on morphine dose for 48 hours, use this dose as the starting point for the morphine wean
  - Consider 72 hours of stabilization if morphine dose >0.4 mg/kg/dose or if adjunctive therapy needed
- Do NOT change the dosing interval during weaning – maintain at Q 3 hour interval

Morphine only:

- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
- Discontinue morphine when the morphine dose is 0.02 mg/kg/dose **OR** 0.05mg/dose whichever is higher

Morphine and Phenobarbital:

- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
- When morphine at 0.3 mg/kg/day (or 0.04 mg/kg/dose) then maintain morphine dose and discontinue phenobarbital, observe for tolerance for 48 hrs
- Resume morphine wean of 10% of the stabilizing dose Q 24-48 hours

Morphine and Clonidine:

- Decrease morphine dose by 10-20% of the stabilizing dose, allowing 24-48 hrs between weans
- Discontinue morphine when the infant has tolerated a morphine dose of 0.02 mg/kg/dose **OR** 0.05mg/dose whichever is higher
- After patient has been stable off morphine for at least 24 hours, clonidine should be discontinued and the patient monitored for a minimum of 48 hours due to risk of rebound hypertension

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Discharge Criteria

Length of hospitalization should be sufficient to detect any subsequent signs of NAS

- Minimum of four to seven days for infants exposed to any opioid
- Small subset of infants may have delayed presentation of NAS

The infant may be discharged when:

- Shows no major signs of withdrawal
- Feeding well
- Sleeping well
- Gaining weight
- Maintaining stable withdrawal scores off of pharmacologic therapy for at least 24 hours

May be discharged with the parents (if the home environment is safe and stable) or to a foster home

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Follow-up

- Close follow-up by pediatrician as outpatient is crucial
- Neurodevelopmental assessments to identify motor deficits and cognitive delays
- Psycho-behavioral assessments to identify hyperactivity, impulsivity, and ADHD in preschool aged children
- Ophthalmologic assessment to look for nystagmus, strabismus, and other visual deficits
- Growth and nutritional assessments to identify failure to thrive/inadequate weight gain and feeding problems
- Family support assessments to exclude ongoing maternal substance abuse and child abuse

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Neurodevelopmental Outcomes

- Often difficult to tease out contribution from substance exposure on developmental outcomes given presence of confounding variables
  - Prematurity, IUGR, continued maternal drug use, low socioeconomic and educational levels, etc
- Studies reported developmental and behavioral concerns in children with prenatal opiate exposure
- Methadone-exposed infants have been found to exhibit increased motor rigidity, dysregulated motor patterns and decreased activity by observation and maternal report
  - Deficits persisted into toddler years and were associated with less social responsivity, shorter attention spans, and poorer social engagement

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Neurodevelopmental Outcomes

- An Australian study showed children with NAS were more likely to be re-hospitalized for maltreatment, trauma, and mental/behavioral disorders (even after accounting for confounding variables)
- Systematic review of case-control studies showed no clinically significant neurobehavioral difference between children exposed to either methadone or heroin, but there was a trend toward poorer outcomes
- Longitudinal study in Norway showed that prenatal opiate and polysubstance exposure was associated with lower IQ at 8 years of age compared to unexposed (controlled for permanent foster/adoptive home placement and earlier cognitive abilities)

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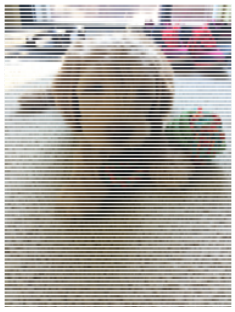
Questions?



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