

Neonatal Abstinence Syndrome (NAS)

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Program for HealthTrust Members



Atlantic
Health System

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Learning Objectives

1. Define the mechanism and clinical presentation of NAS
2. List advantages and limitations of assessment tools utilized for NAS
3. Recognize recommended treatment options for NAS
4. Discuss adjunctive therapies used for NAS
5. State important safety and efficacy parameters associated with the treatment options



Background

- Withdrawal symptoms in newborns due to the combination *in utero* exposure and postnatal cessation
- Sudden discontinuation of prolonged fetal exposure
- Incidence has increased significantly in the past decade
 - Proportionate with the increased use of opioids during pregnancy
- Opioid use antepartum is the most common cause of NAS

Hudak ML, Tan RC. *Pediatrics*. 2012; 129: e540-60.

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Major Drugs of Abuse

Opioids	CNS [†] Stimulants	CNS Depressants	Hallucinogens
Morphine	Amphetamines	Alcohol	Indolealkylamines (e.g. LSD*)
Codeine	Methylphenidate	Barbiturates	Phenylisopropylamines (e.g. MDMA**)
Methadone	Phentermine	Benzodiazepines	Nitrates
OxyCODONE	Cocaine	Cannaboids	Nitrous Oxide
HYDROmorphone	Nicotine		
HYDROcodone			
TraMADol			
Heroin			
Buprenorphine			

*LSD = lysergic acid diethylamide; **MDMA = 3,4-methylenedioxymethamphetamine; †CNS = central nervous system



Risk of Withdrawal

- Type and dose of opioid
- Timing and duration of exposure
- Maternal risk factors
- Placental opioid metabolism
- Genetic variables
- Neonatal conditions
- Environmental factors

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Outcomes of Maternal Opioid Use

- Fetus
 - Growth restriction
 - Preterm labor
 - Abnormal heart patterns
 - Death
- Newborn
 - Low birth weight
 - Preterm delivery
 - Small head circumference
 - Sleep myoclonus
 - Child maltreatment
 - Visual disturbances



Outcomes of NAS

- Increased risk of birth complications
- Admission to neonatal intensive care unit (NICU)
- Pharmacologic treatment
- Prolonged hospitalization
- Infant development
- Child-safety concerns

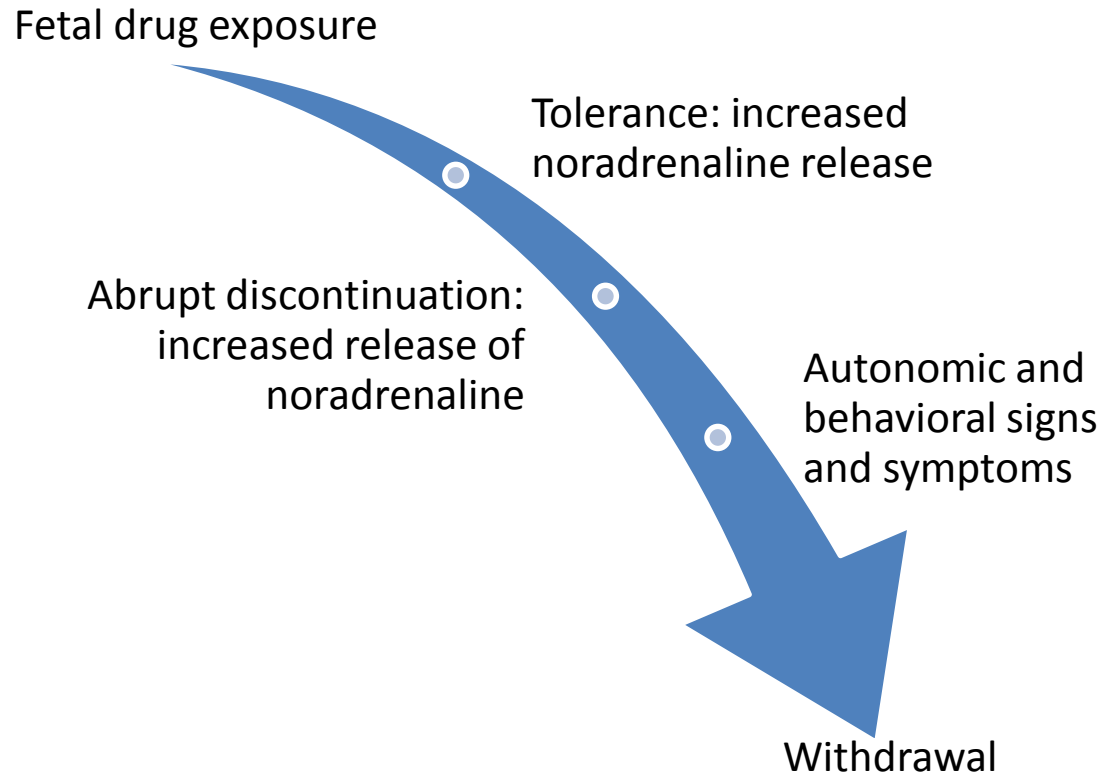


Opioids in Pregnancy

- Lower molecular weight
- Lipophilic substances
- Easily transferable across the placenta
 - Transmission increases with gestation
- Easily transferable across the blood-brain barrier
- Synthetic opioids cross the placenta more easily compared to semisynthetic opioids



Mechanism of Withdrawal



Clinical Manifestations

Autonomic/vasomotor/ respiratory	Gastrointestinal	CNS
Fever	Projectile vomiting	Tremors
Sweating	Regurgitation	High-pitched crying
Nasal stuffiness	Loose/watery stools	Sleep disturbances
Mottling	Weight loss	Increased muscle tone
Tachypnea with or without retractions	Poor feeding/sucking	Frequent yawning/sneezing
	Excessive sucking	Irritability
	Dehydration	Seizures
		Myoclonic jerks

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Timing of Withdrawal

Drug	Onset
Heroin	24 to 48 hours
Opioids	48 to 72 hours
Buprenorphine	36 to 60 hours
Barbiturates	1 to 14 days
Benzodiazepines	Hours to weeks
SSRIs*	24 to 48 hours
Methamphetamines	24 hours
Cocaine	48 to 72 hours
Nicotine	24 to 48 hours
Alcohol	3 to 12 hours

*SSRI = selective serotonin reuptake inhibitor

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Assessment

- Determine severity of signs and symptoms
- Provide guidance for pharmacologic therapy
- Facilitate weaning
- Withdrawal scoring systems
 - Finnegan Scoring Tool
 - The Neonatal Abstinence Scoring System
 - Lipsitz Scoring Tool
 - The Neonatal Drug Withdrawal Scoring System
 - Modified Finnegan Scoring Tool
 - MOTHER NAS Scale



Finnegan Scoring Tool

System	Signs and Symptoms	Score
Metabolic/vasomotor/ respiratory	Sweating	1
	Fever < 101°F (39.3°C)	1
	Fever > 101°F (39.3°C)	2
	Frequent yawning	1
	Mottling	1
	Nasal stuffiness	1
	Sneezing (> 3 to 4 times/interval)	1
	Nasal flaring	2
	Respiratory rate > 60 breaths/min Respiratory rate > 60 breaths/min with retractions	1 2

Finnegan LP, Connaughton JF Jr, Kron RE, et al. *Addict Dis.* 1975; 2: 141-58.
Hudak ML, Tan RC. *Pediatrics.* 2012; 129: e540-60.



Finnegan Scoring Tool

System	Signs and Symptoms	Score
Gastrointestinal	Excessive sucking	1
	Poor feeding	2
	Regurgitation	2
	Projectile vomiting	3
	Loose stools Watery stools	2 3



Finnegan Scoring Tool

System	Signs and Symptoms	Score
Central Nervous	High pitched cry	2
	Continuous high pitched cry	3
	Sleeps < 1 hour after feeding	3
	Sleeps < 2 hours after feeding	2
	Sleeps < 3 hours after feeding	1
	Hyperactive Moro reflex	1
	Markedly hyperactive Moro reflex	2
	Mild tremors disturbed	1
	Moderate-severe tremors disturbed	2
	Mild tremors undisturbed	3
	Moderate-severe tremors undisturbed	4
	Mild increased muscle tone	2
	Excoriation (specific area)	1
Myoclonic jerks	3	
Generalized convulsions	3	



Lipsitz Scoring Tool

	Scoring Categories			
Signs	Score 0	Score 1	Score 2	Score 3
Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate/marked increase when undisturbed; stop when fed or cuddled	Marked increase or continuous even when undisturbed; going on to seizure-like movements
Irritability (excessive crying)	None	Slightly increased	Moderate to severe irritability when disturbed or hungry	Marked irritability even when undisturbed
Reflexes	Normal	Increased	Markedly increased	
Stools	Normal	Explosive, but frequency ≤ 8 /day	Explosive; > 8 /day	
Muscle Tone	Normal	Increased	Rigidity	
Skin Abrasions	No	Redness of elbows, heels, pressure points when supine	Breakdown of skin at pressure points	
Respiratory Rate (bpm)	< 55	55 to 75	76 to 95	
Repetitive Sneezing	No	Yes		
Repetitive Yawning	No	Yes		
Forceful Vomiting	No	Yes		
Fever $> 38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$	No	Yes		
Total Score				



Withdrawal Scoring Systems

Tool (year)	No. of Items	Score Range	Score for Treatment
Finnegan Neonatal Abstinence Scoring Tool (1975)	21	0 to 62	≥ 8 on three consecutive evaluations
Lipsitz Neonatal Drug Withdrawal Scoring System (1975)	11	0 to 20	≥ 4
MOTHER NAS Scale (2010)	19	0 to 42	9; rescore before initiation of drug treatment
Finnegan Neonatal Abstinence Syndrome Scale – Short Form (2013)	7	0 to 16	≥ 8



Withdrawal Scoring Systems

Tool (year)	Comments
Finnegan Neonatal Abstinence Scoring Tool (1975)	<ul style="list-style-type: none"> - Most commonly utilized scoring tool - Lengthy/complex - Less practical - Internal consistency
Lipsitz Neonatal Drug Withdrawal Scoring System (1975)	<ul style="list-style-type: none"> - Simplistic/sensitive - Does not address reliability - No item definitions provided
MOTHER NAS Scale (2010)	<ul style="list-style-type: none"> - Modified version of Finnegan Scoring Tool - Proper instructions - Protocol for pharmacologic treatment - More practical - Internal consistency
Finnegan Neonatal Abstinence Syndrome Scale – Short Form (2013)	<ul style="list-style-type: none"> - Rapid assessment - Limited items - Strong correlation with original Finnegan Scoring Tool - Inadequate for rapidly escalating signs and symptoms - Requires further testing

Supportive Care Treatment

Swaddling and/or
rocking

Minimizing sensory
and/or
environmental
stimulation

Music and massage
therapy

Temperature
stability

Breastfeeding and
frequent feeds



Pharmacologic Treatment

- Drug withdrawal is a self-limiting process
- Indications
 - Newborns at high risk of withdrawing
 - Score > 8 on the Finnegan Scoring System
 - Score > 4 on Lipsitz Tool
 - Newborns who failed supportive care treatment
- Purpose
 - Relieve moderate to severe signs of NAS
 - Prevent complications
 - Provide comfort

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Pharmacologic Treatment

- No universally accepted standard of care
 - Dose based on weight vs severity of symptoms
 - Threshold for initiating treatment
 - Starting doses
 - Weaning protocols
 - Adjunctive medications
- Advantage
 - Short term improvement of clinical signs
- Limitations
 - Prolong drug exposure
 - Prolong duration of hospitalization
 - Decrease maternal-infant bonding

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Patient Case

Baby girl born at 39 + 3 weeks gestational age; 2495 grams

Maternal History

- History of opioid abuse
- GBS positive
- HIV, Rubella, RPR, HBsAG negative

Maternal Medications

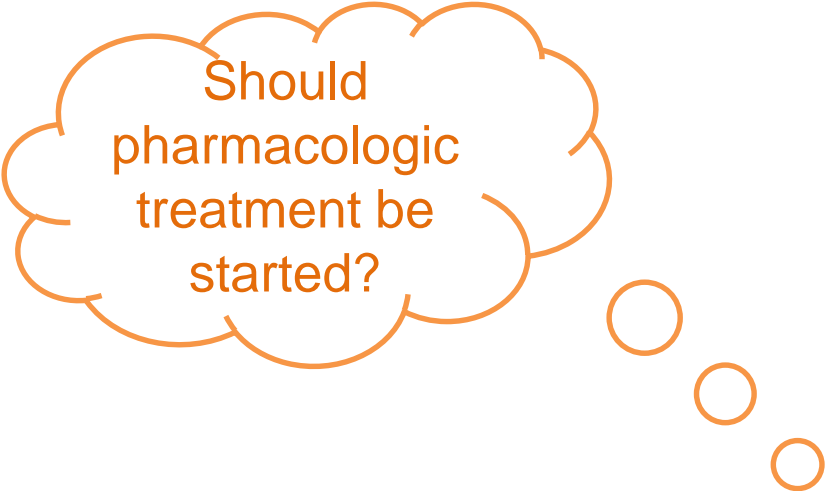
- Folic acid, prenatal vitamins, morphine

Delivery History

- Intrapartum cefazolin 2 gm IV once



Patient Case



Should pharmacologic treatment be started?

Vitals

- Heart rate: 170 beats/min
- Blood pressure: 57/26 mmHg
- Respiratory rate: 66 breaths/min
- Temperature: 37.8°C

Physical Exam

- Neuro: mild tremors, undisturbed
- Heart: tachycardic
- Lungs/thorax: tachypneic
- HEENT: within normal limits
- Activity and reflexes: markedly hyperactive Moro reflex
- Skin: sweating



Pharmacologic Therapies

- Paregoric
- Tincture of opium
- Morphine
- Methadone
- Buprenorphine
- Adjunctive agents
 - PHENobarbital
 - CloNIDine
 - Benzodiazepines
 - DiazePAM, LORazepam
 - ChlorproMAZINE

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Paregoric

- Earliest opioid used
- Anhydrous morphine available as 0.4 mg/mL
- Decreases neuronal activity
- No longer recommended
 - Noscapine, papaverine, camphor, ethanol, anise oil, benzoic acid, and glycerin

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Tincture of Opium

- Contains 10 mg/mL opium
- Contains fewer toxic additives than paregoric
- Institute for Safe Medication Practice (ISMP) safety alerts
 - Contains ethanol
 - Contains multiple narcotic alkaloids
 - Dilution required to produce 0.4 mg/mL morphine equivalence
- Not commonly used

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Morphine

- Most frequently used agent
- Mu-opioid receptor agonist
- Short half-life
- Oral solution
 - Dilution to 0.4 mg/mL recommended
- ISMP safety alert
- Advantages
 - Easily titratable
 - No ethanol
- Limitations
 - Increased risk of sedation, respiratory depression, and constipation
 - Prolonged hospital stay

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Methadone

- Alternative to morphine
- Mu-opioid receptor agonist and NMDA receptor antagonist
- Long half-life; variable
- Advantages
 - No dilution required
 - Consistent blood concentration
 - Less frequent dosing
- Limitations
 - Risk of drug accumulation
 - Prolonged hospital stay
 - Contains ethanol

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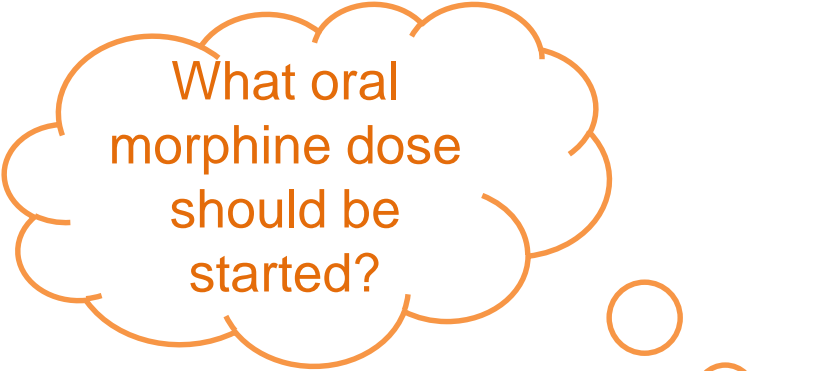
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Back to the Patient



What oral morphine dose should be started?

Despite optimal supportive care, the next Finnegan Score was 10. The plan for the newborn is to start on morphine therapy to help with her NAS.

Weight = 2.495 kg

Recommended dosing:

- Morphine 0.05 mg/kg/dose po every 3 hours
- Morphine 0.125 mg po every 3 hours



Buprenorphine

- Newer option
- Partial mu-opioid receptor agonist
- Given sublingually
 - Intravenous injection
 - Sublingual tablet
 - Compounded to an extemporaneous oral solution
 - 75 mcg/mL
- Advantages
 - Shorter duration of treatment
- Limitations
 - Contains ethanol

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Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

- **Objective**: to determine duration of treatment in infants with NAS comparing sublingual buprenorphine with oral morphine
- **Design**: prospective, double-blind, double-dummy, single center, randomized clinical trial
- **Interventions**
 - Sublingual buprenorphine (n = 33): 0.075 mg/mL
 - Oral morphine (n = 30): dose based on the center standard-of-care morphine protocol
 - PHENobarbital; provided if given maximum dose of opioid reached
 - Loading dose: 20 mg/kg po
 - Maintenance dose: 5 mg/kg po daily



Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

- Primary outcome: duration of treatment
- Secondary outcomes
 - Length of hospital stay
 - Use of adjunct PHENobarbital
 - Adverse events



Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome – BBORN Trial

▪ Results

Outcome	Buprenorphine (n = 33)	Morphine (n = 30)	95% CI	P-value
Median duration of treatment; days	15	28	-13 (-21 to -7)	< 0.001
Median length of hospital stay; days	21	33	-12 (-22 to -7)	< 0.001
Use of adjunct PHENobarbital; n (%)	5 (15)	7 (23)	---	0.36
Adverse events	13 events in 7 patients	10 events in 8 patients	---	0.79

▪ Conclusion

- Not completely clear how buprenorphine allows for shorter duration of treatment than morphine



PHENobarbital

- Non-opioid drug of choice
- Enhances gamma-amino butyric acid (GABA)
 - CNS depression
- Long acting barbiturate
- Monotherapy or adjunct therapy
- Advantages
 - Adjuvant in those withdrawing from poly drug abuse
 - Lower doses of morphine or methadone
- Limitations
 - Does not prevent seizures
 - Ineffective for gastrointestinal symptoms
 - Central nervous system depression
 - Impairment of sucking reflex
 - Cognitive impairment
 - Contains ethanol (unless compounded from tablets)

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CloNIDine

- Centrally acting α_2 -adrenergic receptor agonist
- Adjunct therapy
- Advantages
 - Adjuvant in those withdrawing from poly-drug abuse
 - Shorter duration of treatment
 - Lower doses of morphine or methadone
- Limitations
 - Risk of hypotension and bradycardia
 - Must be weaned off slowly

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CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- **Objective**: to compare the efficacy of cloNIDine versus PHENobarbital in reducing morphine sulfate treatment days for NAS
- **Design**: prospective, non-blinded, single center, randomized clinical trial
- **Interventions**
 - Morphine sulfate + cloNIDine (n = 34)
 - Morphine sulfate + PHENobarbital (n = 34)
 - Dosing protocol utilized
 - Based on Finnegan Score



CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- Primary outcome: treatment days with morphine sulfate
- Secondary outcomes
 - Mean total morphine sulfate dose
 - Outpatient PHENobarbital days
 - Adverse events
 - Treatment failure
 - Mortality in the hospital
 - Readmission within 1 week post discharge



CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- Results

Univariable	PHENobarbital (n = 34)	CloNIDine (n = 34)	P-value
Morphine sulfate; days (95% CI)	12.4 (10.1 to 14.7)	19.5 (15.7 to 23.2)	0.001
Mean total morphine sulfate dose; mg/kg (95% CI)	3.8 (2.9 to 4.7)	6.7 (5.1 to 8.3)	0.002



CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

- Results continued

Multivariable	PHENobarbital (n = 34)	CloNIDine (n = 34)	P-value
Morphine sulfate; days (95% CI)	13.6 (11.0 to 16.1)	18.2 (14.9 to 21.5)	0.037
Mean total morphine sulfate dose; mg/kg (95% CI)	4.6 (3.8 to 5.4)	5.7 (4.7 to 6.8)	0.069



CloNIDine versus PHENobarbital in Reducing Neonatal Morphine Sulfate Therapy Days for Neonatal Abstinence Syndrome

▪ Results continued

- Post-discharge PHENobarbital was continued for an average of 3.8 months (range 1 to 8 months)
- No difference in adverse events
- No difference in treatment failure
- No inpatient mortality
- No readmission within 1 week post discharge

▪ Conclusion

- PHENobarbital as an adjunct shortened length of inpatient treatment days with morphine compared to cloNIDine
- Overall length of NAS treatment is shorter with cloNIDine since no outpatient treatment is required



Morphine versus CloNIDine for Neonatal Abstinence Syndrome

- **Objective**: to determine whether cloNIDine treatment for NAS would result in better neurobehavioral performance compared to morphine
- **Design**: randomized, double-blind trial
- **Interventions**
 - Morphine (n = 15)
 - Starting dose of 0.4 mg/kg/day po q3h
 - CloNIDine (n = 16)
 - Starting dose of 5 mcg/kg/day po q3h



Morphine versus CloNIDine for Neonatal Abstinence Syndrome

▪ Outcomes

- Neurobehavioral performance
 - Measured via the NICU Network Neurobehavioral Scale (NNNS)
 - NNNS administered at 1 week and 2 to 4 weeks after treatment initiation
- Inpatient treatment duration
- Outpatient treatment duration



Morphine versus CloNIDine for Neonatal Abstinence Syndrome

▪ Results

- No difference in NNNS scores between morphine and cloNIDine at 1 week and 2 to 4 weeks after treatment initiation
- Morphine-treated infants showed no difference in any areas from the first to the second assessment
- CloNIDine-treated infants showed significant improvement in areas of attention, handling, arousing, excitability, and lethargy from the first to the second assessment



Morphine versus CloNIDine for Neonatal Abstinence Syndrome

▪ Results

- Significant difference in duration of inpatient treatment

	Morphine (n = 15)	CloNIDine (n = 16)	P-value
Median (range); days	39 (26 to 89)	27.5 (18 to 107)	0.02

- Significant difference in duration of outpatient treatment

	Morphine (n = 15)	CloNIDine (n = 16)	P-value
Median (range); days	26 (16 to 57)	13.5 (6 to 71)	0.005

▪ Conclusion

- Use of cloNIDine as monotherapy may be considered
- Larger randomized clinical trials are needed



Benzodiazepines

- GABA receptor agonist
- Long half-life
- Limitations
 - Central nervous system depression
 - Impairment of sucking reflex
 - Lack of efficacy
 - Safety issues
 - Side effects
- Not recommended

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ChlorproMAZINE

- Phenothiazine antipsychotic; dopamine receptor antagonist
- Long half-life
- Limitations
 - Central nervous system depression
 - Impairment of sucking reflex
 - Lack of efficacy
 - Safety issues
 - Side effects
- Not recommended



Pharmacologic Therapy Protocols

	Hall et al.	Patrick et al.
Objective	To identify pharmacologic treatment strategies for NAS associated with optimal short-term outcomes	To evaluate if standardized care for infants with NAS was associated with improved outcomes
Design	Multicenter, cohort analysis, n = 547	Multicenter, cohort analysis, n = 3458
Intervention(s)	Presence of established NAS weaning protocol arm (n = 130) Absence of established NAS weaning protocol arm (n = 417)	Adaptation of standardized institutional policy for NAS (n = 3458)
Outcomes	Opioid treatment duration Length of stay	Length of treatment Hospital length of stay
Results	Significantly shorter: Duration of opioid treatment; (17.7 vs 32.1 days, $p < 0.001$) Length of stay; (22.7 vs 32.1 days, $p = 0.004$)	NAS-focused policies increased; 3.7 to 5.1 ($p < 0.001$) Decreased length of treatment; 16 to 15 days ($p = 0.02$) Decreased hospital length of stay; 21 to 19 days ($p = 0.002$)

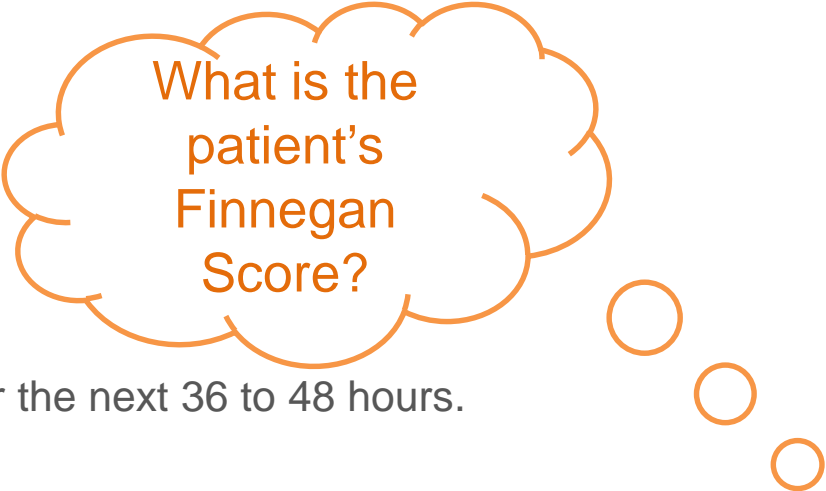


Morphine versus CloNIDine for Neonatal Abstinence Syndrome Weaning Protocol

- Finnegan Scoring Tool
- Morphine was increased by 25% of the initial dose every 24 hours until scores were < 8 and symptoms were controlled
 - Maximum dose of 1 mg/kg/day
- After 48 hours of symptom control, all scores < 8 , morphine was decreased by 10% once every other day
- Once the dose was < 0.1 mg/kg/day, morphine was discontinued
- Observed for 48 hours after the last dose of trial medication
- If symptoms reoccurred, previous dose was administered
 - Weaning resumed after 48 hours



Back to the Patient



What is the patient's Finnegan Score?

Newborn improved symptomatically over the next 36 to 48 hours.

Vitals

- Heart rate: 100 beats/min
- Blood pressure: 60/29 mmHg
- Respiratory rate: 50 breaths/min
- Temperature: 37.0°C

Physical Exam

- Neuro: mild tremors, disturbed
- Heart: within normal limits
- Lungs/thorax: within normal limits
- HEENT: within normal limits
- Activity and reflexes: hyperactive moro reflex
- Skin: within normal limits

How should the patient be weaned off of morphine?



Follow-up

- Psycho-behavioral assessment
 - Hyperactivity, impulsivity, and attention-deficit
- Ophthalmologic assessment
 - Nystagmus, strabismus, visual deficits
- Growth and nutritional assessment
- Family support assessment



Long-term Outcomes

- Difficult to evaluate
 - Confounding variables
- At risk of motor deficits, cognitive delays, or relative microcephaly



Summary

- Implementation of a standardized protocol at each institution is the optimal way to approach pharmacologic treatment for patients with NAS
- Buprenorphine is an emerging new therapy that may be considered for first line treatment for patients with NAS
- Larger randomized clinical trials need to be conducted to determine the role of clonidine as monotherapy
- Important safety and preparation considerations associated with pharmacologic therapy when treating patients with NAS



Poll Question #1

1. Signs and symptoms of NAS may be classified by the following affected systems except:
 - a. Neurologic
 - b. Renal
 - c. Gastrointestinal
 - d. Autonomic



Response Question #1

1. Signs and symptoms of NAS may be classified by the following affected systems except:
 - a. Neurologic
 - b. Renal**
 - c. Gastrointestinal
 - d. Autonomic



Poll Question #2

2. The Finnegan Scoring System has ____ main categories and ____ variables

- a. 3, 12
- b. 3, 21
- c. 12, 3
- d. 21, 3



Response Question #2

2. The Finnegan Scoring System has ____ main categories and ____ variables

- a. 3, 12
- b. 3, 21**
- c. 12, 3
- d. 21, 3



Poll Question #3

3. Which of the following is most frequently used for the treatment of NAS

- a. Morphine
- b. Methadone
- c. Buprenorphine
- d. CloNIDine



Response Question #3

3. Which of the following is most frequently used for the treatment of NAS

- a. **Morphine**
- b. Methadone
- c. Buprenorphine
- d. CloNIDine



Poll Question #4

4. A disadvantage of using cloNIDine for adjunctive treatment is
 - a. Only available in oral formulation
 - b. Does not exhibit the sedative or respiratory depressive properties of opioid or barbiturate agents
 - c. Lowers blood pressure
 - d. Contains alcohol



Response Question #4

4. A disadvantage of using cloNIDine for adjunctive treatment is
- a. Only available in oral formulation
 - b. Does not exhibit the sedative or respiratory depressive properties of opioid or barbiturate agents
 - c. **Lowers blood pressure**
 - d. Contains alcohol



Poll Question #5

5. Which of the following must be monitored in neonates while on morphine therapy for NAS
- a. Sedation
 - b. Respiratory depression
 - c. Constipation
 - d. All of the above



Response Question #5

5. Which of the following must be monitored in neonates while on morphine therapy for NAS
- a. Sedation
 - b. Respiratory depression
 - c. Constipation
 - d. **All of the above**



Thank you...

