Clonidine for Opioid Related Neonatal Abstinence Syndrome: Is Clonidine the New Alpha-Male of Adjunct?

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Learning Objectives

1. Describe neonatal abstinence syndrome.
2. Discuss the effects of withdrawal in a neonate.
3. Compare alternative adjunctive therapies for neonatal abstinence syndrome.
4. Evaluate literature assessing the use of clonidine in neonatal abstinence.
I. Background of Neonatal Abstinence Syndrome

1. Definition and epidemiology
   a. "Clinical diagnosis resulting from abrupt discontinuation of chronic fetal exposure to substances used or abused by the mother during pregnancy."\(^1\)
      i. Passively – in utero exposure through maternal use
      ii. Iatrogenically – withdrawal of medications used for sedation and analgesia
   b. Incidence has significantly increased of the last decades.
      i. Increase in NAS cases from 1.2 to 3.4 diagnoses per 1000 live births from 2000 to 2009 respectively.\(^2\)
      ii. Increase in number of mothers using or dependent on opiates from 1.19 to 5.63 from 2000 to 2009 respectively.\(^2\)
      iii. 13,539 cases of NAS in 2009
         1. Approximately one newborn with NAS each hour\(^3\)
   c. In 2013, about 24.6 million American \(\geq\)12 years old used illicit substances in the past month\(^3\).
      i. Reports include non-medical use of illicit substances, which include LSD, PCP, peyote, mushrooms, ecstasy, marijuana, cocaine, heroin, stimulants, and sedatives.
   d. 5.4% of pregnant women were current users of illicit drugs in 2013.

2. Economic Impact
   a. As the number of NAS cases has increased so has the expenditure.
   b. Healthcare expenditure increased from $190 million to $720 million from 2000 to 2009.\(^2\)
      i. The average length of stay has not fluctuated with the average still around 16 days.\(^2,4,5\)
   c. NAS has a higher cost per stay at an average of $53,400 in 2009 compared to $9,500 for non-NAS stays.

Table 1: Admissions \(>\) 12 years old according to primary substance of abuse 2012\(^3,11\)

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<thead>
<tr>
<th>Substance</th>
<th>All admissions</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>Alcohol only drug</td>
<td>3761</td>
<td>1811</td>
<td>1950</td>
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<tr>
<td>Any other opioid</td>
<td>5200</td>
<td>2670</td>
<td>2530</td>
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<tr>
<td>Cocaine</td>
<td>9674</td>
<td>4877</td>
<td>4797</td>
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</table>

Table 2: Average hospital charge and length of stay for neonatal abstinence syndrome vs all other US births\(^2\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Neonatal Abstinence Syndrome</th>
<th>All Other US Births</th>
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<td>2000</td>
<td>39,400 (34,400-46,400)</td>
<td>47,900 (40,800-55,100)</td>
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<td>44,600 (40,400-48,900)</td>
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<tr>
<td>2006</td>
<td>53,400 (49,000-57,700)</td>
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<td>2009</td>
<td>66,000 (58,000-73,000)</td>
<td>73,000 (69,000-76,000)</td>
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</table>
3. **History of NAS**

![Timeline of opiates and NAS](image)

**Pathophysiology**

a. Effects of acute opiate use on neurotransmitters
   i. Increased dopamine
   ii. Increased serotonin
   iii. Decrease in GABA
   iv. Decrease in norepinephrine
   v. Decrease corticotropin-releasing hormone

b. Mechanism of withdrawal
   i. Acute exposure decreases cAMP and neurotransmitter production
   ii. Body compensates with chronic use and increases production
   iii. Discontinuation causes increase in cAMP and neurotransmitter production

c. Opiates crossing the placenta
   i. Small molecular weight
   ii. Less protein binding
   iii. Lipophilic
   iv. P-gp efflux pumps begin decreasing at 35 weeks gestation
      1. Slower removal of drug
      2. Exposure later in pregnancy leads to increased fetal exposure

d. Prolonged half-life (T½) of opiates in the fetus
   i. Morphine
      1. \( T_\frac{1}{2} = 9 \) hours in premature neonates
      2. \( T_\frac{1}{2} = 6.5 \) hours in term neonates
   ii. Methadone
      1. \( T_\frac{1}{2} = 3.8-68 \) hours in neonates
   iii. Heroin
      1. \( T \frac{1}{2} = 30 \) minutes
      2. Active metabolite 6-monooacetylmorphine further converted to morphine

e. Prognosis of neonates with intrauterine exposure
   i. Increase in psychomotor and neurologic abnormalities at one year of age
      1. Decrease in locomotor and intellectual development

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1. 1892: Series of 12 infants with neonatal withdrawal which led to nine deaths. Trial of paregoric.
2. 1903: Morphine treatment for neonates reported
3. 1971: Methadone withdrawal in five neonates
4. 1804: Morphine isolated
5. 1817: Marketed as analgesic
6. 1827: Commercial production
7. 1853: Hypodermic needle developed
8. 1874: Heroin synthesized
9. 1898: Commercial production
10. 1903: Hypodermic needle developed
11. 1937: Methadone developed
12. Figure 2: Timeline of opiates and NAS
13. Figure 3: Steps to withdrawal
II. Clinical Presentation

1. Signs and symptoms
   a. Symptom onset depends on:
      i. Last in-utero exposure
      ii. Substance used in-utero
      iii. Gestational age
      iv. Maternal use of multiple substances
   b. Typical time to withdrawal symptom onset
      i. Heroin – within first 24-48 hours
      ii. Methadone – 48-72 hours
      iii. Prescription opioids – 36-72 hours
   c. Symptoms
      i. Neurologic
      ii. Gastrointestinal
      iii. Autonomic
   d. If left untreated there is an increased risk of sudden infant death syndrome (SIDS)

2. Diagnosis
   a. Diagnosis is based on two major factors
      i. Maternal history
      ii. Neonatal signs and symptoms
   b. Testing (see appendix page A7)
      i. Maternal drug screen
      ii. Newborn urine screen
      iii. Meconium analysis
   c. Testing should be performed if:
      i. Mother self-reports use of substances
      ii. Mother has a known history
      iii. Signs are present and history is unknown

3. Assessment
   a. Tools we have for assessing and guiding therapy (see appendix page A4)
      i. Original Finnegan Scale (see appendix page A5)
         1. 31 item list evaluating symptoms and severity
         2. Comprehensive list evaluating multiple symptoms
         3. Takes more time to complete but more inclusive
      ii. Lipsitz Neonatal Drug-Withdrawal Scoring System
         1. 11 item scale with scoring ranging from 0-3 based on severity
         2. Easily administered but contains subjective areas
         3. Not as comprehensive
         4. No longer recommended for scoring
      iii. Modified Finnegan Scale
         1. 21 item list similar to the Finnegan scale
         2. Decreased from 31 due to redundancies in the previous version
         3. Most commonly used and widely accepted scoring system
         4. Gold standard
III. Management

1. **Goals**
   a. Ensure safe and comfortable withdrawal
   b. Maintain appropriate nutritional intake
   c. Ensure appropriate fluid status
   d. Ensure appropriate adaptation to the environment
   e. Prevent complications

2. **Guideline Recommendations**
   a. Overview
      i. Non-pharmacologic
         1. Shown effective in managing mild cases (MFS < 8)
         2. Should be used at every stage of therapy
      ii. First line pharmacologic
         1. Opiate replacement with morphine
      iii. Adjunctive with non-opioid treatment
         1. Phenobarbital
         2. Clonidine
   b. Ontario guidelines
      i. Assess using MFS
      ii. Non-pharmacologic options are first line
      iii. Initiate oral morphine if MFS ≥ 8
         1. Titrate dose to maintain scores < 8
      iv. Consider clonidine if morphine dose reaches 1mg/kg/day
   c. Australian guidelines
      i. First determine risk and begin scoring
      ii. Begin non-pharmacologic measures
      iii. Opiate dependent mothers?
         1. Yes – morphine
         2. No – Phenobarbital
      iv. Start phenobarbital as adjunctive if morphine dose of 1mg/kg/day is reached.
   d. American Academy of Pediatrics
      i. Determine risk of NAS and begin scoring if they are at risk
      ii. Start non-pharmacologic treatment
      iii. Only exposed to opiates?
         1. Yes – morphine
         2. No – phenobarbital
      iv. Augment with phenobarbital or clonidine if dose of 1.3 mg/kg/day of morphine needed

3. **Non-Pharmacologic**
   a. Swaddling
   b. Rocking
   c. Maintain extremities at midline
   d. Pacifiers
   e. Decreasing external stimuli
   f. Maintain temperature stability

4. **First Line Pharmacologic Therapy (see appendix page A6)**
   a. Oral morphine is the preferred agent
      i. Shorter duration of action when compared with methadone
      ii. Less alcohol content compared to diluted tincture of opium
b. Methadone
   i. An option but less preferred than morphine
   ii. Long half-life with difficult titration

c. Buprenorphine
   i. Lack of evidence to support use in neonates

5. **Adjunctive Therapy**\textsuperscript{15,24,25}
   a. Clonidine
      i. Mechanism
         1. Alpha-2 agonist that works at the presynaptic terminals in the medulla causing an inhibition of sympathetic outflow.
      ii. Effects on NAS
         1. Inhibition of sympathetic outflow decrease epinephrine and norepinephrine
         2. Decreases autonomic symptoms such as:
            1) Tachycardia
            2) Agitation
            3) Hypertension
            4) Sweating
      iii. Pharmacokinetics
         1. Absorption = 75-90%
         2. Protein binding = 20-40%
         3. Half-life = 44-72 hours\textsuperscript{26}
            1) Increased due to decreased clearance and metabolism\textsuperscript{27}
      iv. Common side effects
         1. Hypotension
         2. Bradycardia
         3. Rebound hypotension with abrupt discontinuations

b. Phenobarbital
   i. Mechanism
      1. Augments receptors and promotes binding of GABA to cause CNS depression
   ii. Effects in NAS
      1. Causes decreased excitability
   iii. Pharmacokinetics
      1. Absorption= 70-90%
      2. Half-life = 45-100 hours
   iv. Common side effects
      1. Sedation
      2. Bradycardia
      3. Hyperactivity
   v. Long term side effects
      1. Decreased cognitive performance that lasted years following discontinuation\textsuperscript{28}
### IV. Literature Evaluation


#### General Study Overview

<table>
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<tr>
<th>Objective</th>
<th>To determine if oral clonidine plus diluted tincture of opium (DTO) would reduce the duration of opioid detoxification for neonatal abstinence syndrome compared with DTO alone</th>
</tr>
</thead>
</table>

#### Methods

| Trial Design |  
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              | • Randomized, double blind, placebo controlled, intention to treat, multi-center, parallel, safety/efficacy study |

| Inclusion Criteria |  
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    | • Age of 0-14 days  
|                    | • ≥ 35 weeks gestation  
|                    | • Prenatally exposed to opioids  
|                    | • Severe NAS defined by 2 consecutive Modified Finnegan Scores ≥ 9 |

| Exclusion Criteria |  
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    | • <35 weeks gestation  
|                    | • Intrauterine growth retardation defined as <5th percentile of gestational age  
|                    | • Postnatal treatment with barbiturate or benzodiazepines  
|                    | • Major congenital anomalies  
|                    | • Breastfed infants  
|                    | • Major illnesses requiring oxygen therapy, IV fluids, or medications |

| Intervention | Two arms – clonidine + DTO vs placebo + DTO  
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DTO dose    | • 1:25 dilution with dose = 0.4 mg/ml of morphine equivalents  
|            | • Patients started at 0.2 ml every 4 hours and increased dose by 0.1 ml increments following 2 consecutive MFSs ≥9  
|            | • Patients switched to every 3 hours dosing once reaching 0.5 ml until symptoms were controlled (MFSs <9)  
|            | • Patients were deescalated once the daily MFSs averaged <9 and dose was not increased for 48 hours  
|            | • Dose was deescalated by 0.05 ml every 24 hours as long as symptoms were controlled (uncontrolled = 2 consecutive MFSs ≥9)  
|            | • Considered treatment failure if on max dose (0.9ml q3h) with 2 consecutive MFSs ≥9 Clonidine/matching placebo  
|            | • 1 mcg/kg every 4 hours |

| Outcomes |  
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | • **Primary** – total duration of pharmacotherapy for NAS  
|          | • **Secondary** – amount of DTO required to treat, treatment failure defined as >0.9 mL of DTO every 3 hours, seizures, weight gain, blood pressure differences, weight gain, heart rate, and $O_2$ saturations. |

| Statistical Analysis |  
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | • Required 80 patients to demonstrate a 25% reduction in the primary outcome with 80% power and a 2-sided alpha of 0.05  
|                      | • Continuous variables were analyzed using independent-sample $t$ test (between groups) and a paired-sample $t$-test was used for within group analysis.  
|                      | • Log-rank test for time dependent outcomes  
|                      | • Fischer’s exact test for categorical variables |

#### Results

| Enrollment |  
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|           | • 221 eligible patients  
|           | o 141 not enrolled  
|           | • Infant or mother enrolled in another trial |
- Started on DTO prior to enrollment
- Unavailable to enroll infant
- Maternal Refusal
  - 80 randomized into 2 treatment arms
    - Clonidine + DTO
    - Placebo + DTO

**Baseline characteristics**

Baseline characteristics of infants were similar except birth weight in the clonidine arm was significantly lower (2864 g vs 3047 g). There was also no statistically significant difference in the maternal characteristics (age, years of opioid dependence, use of methadone program, and max methadone dose).

**Treatment Efficacy**

Overall length of DTO therapy was 27% shorter in the clonidine arm (mean 11 days) compared to the placebo group (mean 15 days) despite 7 infants in the clonidine group requiring a restart of DTO upon discontinuation. The infants in the placebo group required higher doses of DTO compared to the clonidine group.

![Graph](image)

Patients experienced severe adverse events such as: death and one episode of supraventricular tachycardia, both of which occurred in the clonidine arm. The one SVT occurrence happened three days following clonidine discontinuation and the three deaths were due to myocarditis, sudden infant death syndrome, and homicide.

**Author’s Conclusions**

Determined the use of clonidine and DTO allowed for less days of therapy compared to DTO alone. In addition, the use of clonidine did not significantly increase cardiovascular events; however, longer trials would be required to assess its long-term safety.

**Discussion**

**Strengths**
- Intention to treat protocol
- Double blinded and placebo controlled

**Limitations**
- Small patient population
- Did not separate outcomes based on substance of abuse

Clonidine provides an alternative to the solitary use of DTO (or morphine equivalent) and can decrease both the amount of opiate used and time of opiate use. Based on this study, infants born to mothers who present with a history of methadone, heroin, or cocaine use should have clonidine considered if appropriate MFSs (≥ 9) are met. It is important to monitor patients for blood pressure decreases upon initiation as well as increases upon discontinuation. Unlike this study, a clonidine taper should be considered before discontinuation for prevention of rebound hypertension and tachycardia.
## General Study Overview

**Objective**
To compare the efficacy of clonidine versus phenobarbital in reducing morphine sulfate treatment days for neonatal abstinence syndrome (NAS)

**Methods**

### Trial Design
Open label, randomized, parallel, safety and efficacy study

### Inclusion Criteria
- 0-15 days of age
- Prenatal exposure to opioids with development of moderate to severe NAS (2 Modified Finnegan Scores > 8)
- Medically stable

### Exclusion Criteria
- Gestational age <35 weeks
- Intrauterine growth retardation (weight < 5th percentile)
- Congenital heart disease
- Congenital anomalies
- Medically unstable
- Exposure to benzodiazepines prenatally

### Intervention
Therapy initiated when 2 MFSs were >8 or 1 was >12

Clonidine and phenobarbital were weaned off after discontinuation of morphine sulfate. Clonidine was weaned every 24 hours. Phenobarbital was weaned every 7 days.

### Outcomes
- Primary – time taken to wean off morphine sulfate
- Secondary – total morphine dose, total phenobarbital days, number of treatment failures, adverse events, mortality in the hospital, and readmission 1 week post-discharge

### Statistical Analysis
- Linear regression to compare time to wean
- Cox proportion hazard to compare study groups
- Fishers exact test for categorical data
- Continuous data was compared using Wilcoxon rank-sum

## Results

### Enrollment
- 146 screened due to maternal opiate use (64 were excluded)
- 82 consented (14 did not have high MFS or were not stable)
- 68 randomized – clonidine (n=34) or phenobarbital (n=34)
- 66 analyzed (2 in phenobarbital arm withdrew consent)

### Baseline Characteristics
Baseline characteristics were similar between the groups, except the clonidine group had a statistically significant elevation in the MFS at baseline.

### Treatment Efficacy
The study showed that patients on phenobarbital experienced significantly less treatment days with morphine (difference of 4.6 days p=0.03); however, the overall duration of NAS treatment was less in the clonidine group. The average morphine dose used was similar between the two groups with no statistical difference (p=0.069).
**Author’s Conclusions**

Concluded that clonidine was a safe and feasible alternative to phenobarbital for the treatment of neonatal abstinence syndrome. While the use of clonidine did not significantly decrease the overall inpatient length of therapy, it was associated with shorter overall duration of NAS treatment compared to phenobarbital.

**Discussion**

**Strengths**

- Strict protocol for therapy and weaning
- No inpatient mortality or readmissions

**Limitations**

- Non-blinded trial with potential for nursing bias
- Patients in the phenobarbital group had lower MFS at baseline compared to the clonidine group
- Patients continued on phenobarbital and stopped clonidine before discharge, which could have increased inpatient stay.
- Used only one hospital’s protocol for phenobarbital

**Discussion**

While the overall length of morphine therapy was significantly shorter in the phenobarbital arm there was an increased length of therapy for NAS since patients on phenobarbital had an average of 3.8 months of therapy after discharge. Patients in the clonidine arm were monitored and weaned off clonidine allowing for adequate discontinuation. Overall, more studies are needed before this information can be applied. However, this study does show that even though the patient may have a longer course of morphine therapy the use of clonidine still saw similar rates of efficacy as phenobarbital.

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**General Study Overview**

**Objective**

Retrospective review to determine if clonidine was a suitable option in the prevention and management of neonatal abstinence syndrome

**Methods**

**Trial Design**

- Retrospective chart review

**Intervention**

Patients received clonidine 0.5 – 1 mcg/kg every 6 hours
5 patients received lorazepam prior to clonidine initiation
1 patient received phenobarbital
1 patient received chloral hydrate

**Results**

**Enrollment**

- 14 patients
- 11 – with long term fentanyl infusion for sedation
- 2 – in utero exposure to methadone
- 1 – in utero exposure to heroin

**Baseline Characteristics**

- Average gestational age 30.1 weeks
- Average NAS score before clonidine 6.4 (range: 0-20)
- 11 patients on long term fentanyl infusion
- 3 patients born to opiate exposed mothers

**Efficacy**

- Average NAS score after clonidine treatment was 1.9
- No adverse events were seen

**Author’s Conclusions**

Clonidine may be a suitable alternative to more traditional agents for prevention or management of NAS. The data from this trial is similar to other trial displaying safety and efficacy; however, it does require larger trials before it can be routinely recommended.

**Discussion**

**Strengths**

- Used as first line
- Patients adequately controlled without need for morphine
Limitations
- Retrospective
- Scores were <8 at time of treatment
- Started treatment before onset of symptoms
- Addition of other sedative agents

Discussion
This very small retrospective study has multiple limitations that should not be overlooked. However, it does provide some evidence that clonidine may control symptoms without morphine. There are more studies needed to show if clonidine can be used as initial therapy.

1. Cochrane Review
   a. Assessed the use of sedatives for the treatment of NAS
      i. Looked at seven studies to assess safety and efficacy
         1. Six studies used phenobarbital
         2. One study used Clonidine (Agthe 2009)
   b. Conclusion
      i. Phenobarbital
         1. Preferred over diazepam
         2. Preferred over chlorpromazine
         3. Combination with opiated had decreased length of stay over opiate therapy alone

   Figure 5: Comparison of phenobarbitone and opiate versus opiate alone on treatment failure

   ii. Clonidine
      1. No statistically significant differences from placebo on treatment failure

   Figure 6: Comparison of clonidine and opiate versus opiate alone on treatment failures

   iii. Overall
      1. Phenobarbital is an option when morphine is not managing the patient.
      2. More studies on clonidine are needed to assess long term outcomes for safety and efficacy.
      3. This review was conducted in 2009 and does not include the study from Surran and colleagues.
V. Conclusions

1. NAS overview
   a. Cases of neonatal abstinence syndrome have increased over the last decade.
   b. If untreated the risk of SIDS and neonatal seizures increases
   c. Identification and prompt assessment of at risk infants is important
   d. Non-pharmacologic measures should be used in all patients
   e. Guidelines recommend the use of appropriate assessment tools for pharmacologic therapy initiation

2. Recommendations
   a. Obtain detailed history
      i. Maternal drug history
         1. Opiate vs non-opiate use
      ii. Time of last use
   b. Begin scoring at 2 hours of life
   c. Initiate non-pharmacologic measures
   d. 2 consecutive MFSs > 8 or 1 MFS > 12 initiate oral morphine
   e. Add clonidine:
      i. Uncontrolled with morphine and polydrug use is not suspected OR
      ii. Morphine dose > 1.3mg/kg/day required\(^1\)

Figure 7: Concluding recommendations
References

3. US Department of Health and Human Services. Results from the 2011 national survey on drug use and health: Summary of national findings. substance abuse and mental health services administration; center for behavioral health statistics and quality. 2011.


## Appendix

### Figure A1: Types of Illicit Drug Use in the Past Month among Females Aged 15 to 44, by Pregnancy Status: Percentages, Annual Averages Based on 2008-2009 and 2010-2011

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</tr>
<tr>
<td>Methamphetamine</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td>0.2</td>
<td>*</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td>0.2</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Estimates in the Total column are for all females aged 15 to 44, including those with unknown pregnancy status.
2. Low precision; no estimate reported.
3. Difference between estimate and 2010-2011 estimate is statistically significant at the 0.05 level.
4. Difference between estimate and 2008-2009 estimate is statistically significant at the 0.01 level.

**NOTE:** Some 2008-2009 estimates may differ from previously published estimates due to updates (see Section B.3 in Appendix B of the Results from the 2011 National Survey on Drug Use and Health: National Findings).

**Sources:** SAMHSA. Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health. 2008-2011.
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Modified Finnegan</th>
<th>F</th>
<th>Lipitz</th>
<th>Symptom if Different from Finnegan</th>
<th>Score if Present</th>
<th>Score if Present</th>
<th>Score if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive high-pitched cry &lt; 5 mins</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td>++</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous high-pitched cry &gt;5 mins</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep &lt;1 hr after feed</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep &lt;2 hrs after feed</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep &lt;3 hrs after feeding</td>
<td>+</td>
<td>1</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypactive active Moro reflex</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markedly hypactive Moro reflex</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>+</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild tremors when disturbed</td>
<td>+</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod/severe tremors when disturbed</td>
<td>+</td>
<td>2</td>
<td>3</td>
<td>+</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild tremors when undisturbed</td>
<td>+</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod/severe tremors when undisturbed</td>
<td>+</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>+</td>
<td>1</td>
<td>2</td>
<td>+</td>
<td>Muscle tone</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Excoration (chin, knees, elbow, toes, nose)</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>Skin abrasions</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Myoclonic jerks (twitching/jerking of limbs)</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised convulsions</td>
<td>+</td>
<td>5</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive sucking</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor feeding</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitation</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Projectile vomiting</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td>+</td>
<td>Vomiting</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loose stools</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td>+</td>
<td>Stools</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Watery stools</td>
<td>+</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever 37.3 to 38.3°C (*1)</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>Fever</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fever 38.4 and above (*2)</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent yawning (&gt;3-4 times scoring interval)</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>Repetitive yawning</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Motting</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneezing (&gt;3-4 times scoring interval)</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>Repetitive sneezing</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasal flaring</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &gt; 60/min</td>
<td>+</td>
<td>1</td>
<td>1</td>
<td>+</td>
<td>Respiratory rate &lt;55/min</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &gt; 60/min &amp; extrusion</td>
<td>+</td>
<td>2</td>
<td>2</td>
<td></td>
<td>Respiratory rate &gt;55-75/min</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Score at which treatment is initiated</td>
<td>≥8</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F = Original Finnegan Scale

(*1) Original Finnegan: Fever <101°F (38.3°C)

(*2) Original Finnegan: Fever >101°F (39.3°C)

Figure A2: Comparison of multiple scoring systems.

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Instructions
- Designed for use with full term opioid-exposed newborns
- Initiate scoring at 2 hours of age and repeat every 2-4 hours prior to a feeding. Do not wait baby to do scoring.
- Total scores for each interval at bottom of column
- Calculate & record 90% of birth weight to use as a reference for weight loss
- Initiate pharmacologic treatment when the average of 3 scores is ≥ 8 or the average of 2 scores, or 2 consecutive scores is ≥ 12
- Score for minimum of 72 hours, 120 hours for methadone exposure. Continue scoring during treatment and weaning.
- Discontinue scoring 48-72 hours after treatment discontinued.

Excessive Cry
- Cry is usually high pitched
- Score 2: Infant cries often and is difficult to console
- Score 3: Infant is inconsolable, even with a pacifier, swaddling or rocking

Sleeping
- Use the longest continuous sleeping time between feedings and scoring periods
- Score 0: Sleeps more than 3 hours continuously
- Score 1: Sleeps 2-3 hours continuously
- Score 2: Sleeps 1-2 hours continuously
- Score 3: Sleeps less than 1 hour continuously

Moro Reflex
- Avoid doing while infant is irritable or crying to insure that the jitteriness, if present, is due to withdrawal, not agitation
- Score 1: Hyperactive Moro Reflex: hyperactive response with excessive abduction at shoulder and extension at elbow with or without tremors
- Score 2: Markedly Hyperactive Moro Reflex: Above response plus marked abduction flexion at elbow with arms crossing to the midline

Tremors
- Involuntary movements that are rhythmic and of equal amplitude.
- Myoclonic jerks are not tremors
- Undisturbed tremors occur in the absence of stimulation
- Disturbed tremors occur with stimulation, i.e. unwrapping a swaddled infant
- Score 1: Mild tremors involve hands or feet only & occur frequently in fussy or crying states and occasionally in quiet alert states
- Score 2: Moderate - severe tremors involve arms or legs and occur consistently and repeatedly in all states

Increased Muscle Tone
- Billet by passively extending and releasing the infant’s arms and legs to assess recoil
- Assess infant at rest and with gentle handling, in quiet alert and mildly fussy states
- Infants experiencing NAS may have fluctuating tone
- Score 1: Increased tone with handling or increased resistance to extension or flexion of limbs with head lag on pull to sit
- Score 2: Increased tone without handling or increased resistance to straightening or bending limbs with or without head lag

Excoriation
- Results from excessive and uncontrolled movements, such as tremors, rubbing. Diaper area excoriation is not included
- Score 1: As long as the excoriation is present
- Score 2: Skin is red, but intact or healing
- Score 3: Skin is broken

Generalized Seizure
- Seizure activity requires notification of the pediatrician immediately
- Score 1: Incidence of seizures as a symptom of NAS is low, but if present

Hyperthermia
- If hyperthermia is present, rule out infection
- Score 1: Axilla temperature of 37.3°C or higher

Yawning
- Score 1: Yawning 4 times or more in a scoring interval

Sweating
- Score 1: Dampens of the infant’s forehead or upper lip providing the infant is not over dressed

Nasal Stiffness
- Score 1: Nasal noise with breathing, not associated with illness

Sneezing
- Score 1: Sneezing 4 times or more in a scoring interval

Tachypnea
- Score 2: Respiratory rate greater than 60 breaths per minute at rest and not fussy or crying
- Rule out other medical conditions

Poor Feeding
- Score 2: Uncoordinated suck/swallow resulting in:
  - Inefficient suck
  - Inefficient sucking pattern: short bursts with weak suck despite excessive sucking prior to feeding
  - Maladaptive tongue position: tongue thrusting, tongue above nipple, formula loss at sides of mouth
  - Gulping or clicking noise with sucking
  - Takes frequent breaks from feeding to breathe, burp or spit up

Vomiting
- Score 1: Vomits 1 whole feed, or two or more times during a feed, not associated with burping

Loose Stools
- Score 2: ≥ 1 liquid or semi solid stool or liquid stool with our without a water ring on diaper

Weight Loss / Failure to Thrive
- Use work space at top of form. Weight infant once a day
- Score 2:
  - Current weight loss is greater than 10% of birth weight
  - Failure to regain birth weight by 10 days of age
  - Daily weight gain of less than 20 gms/day after birth weight regained

Irritability
- Infant is irritable or fussy, particularly with light touch or handling despite attempts to console, but may not cry excessively or at all.
- Observe for grimacing, sensitive to touch, light or sound, gaze aversion, etc. with or without crying
- Score 2: Displays 2-3 signs of irritability and is consoled only with intervention after time
- Score 3: No amount of consoling reduces the symptoms of irritability

Figure A2: Guide to using the Modified Finnegan Scale

M. Flynt 2015
### Table 4: Neonatal Drug-Withdrawal Scoring System

<table>
<thead>
<tr>
<th>Signs</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremors (muscle activity of limbs)</td>
<td>Normal</td>
<td>Minimally increased when hungry or disturbed</td>
<td>Moderate or marked increase when undisturbed; subsides when fed or held snugly</td>
<td>Marked increase or continuous even when undisturbed, going on to seizure-like movements</td>
<td></td>
</tr>
<tr>
<td>Irritability (excessive crying)</td>
<td>None</td>
<td>Slightly increased</td>
<td>Moderate to severe when disturbed or hungry</td>
<td>Marked even when undisturbed</td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
<td>Increased</td>
<td>Markedly increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steats</td>
<td>Normal</td>
<td>Explosive, but normal frequency</td>
<td>Explosive, more than 6 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Increased</td>
<td>Rigidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin abrasions</td>
<td>No</td>
<td>Redness of knees and elbows</td>
<td>Bruising of the skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate/minute</td>
<td>&lt;55</td>
<td>55–75</td>
<td>76–95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetitive sneezing</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetitive yawning</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure A4: Neonatal Drug Withdrawal Scoring System**

<table>
<thead>
<tr>
<th>First line</th>
<th>Mechanism</th>
<th>Side Effects</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluted tincture of opium</td>
<td>Mu agonist</td>
<td>Respiratory depression, constipation, sedation</td>
<td>Recommended by American Academy of Pediatrics</td>
<td>Contains alcohol, &gt;10 opioid alkaloids</td>
</tr>
<tr>
<td>Morphine</td>
<td>Mu agonist</td>
<td>Respiratory depression, constipation, sedation</td>
<td>Ease of titration</td>
<td>Frequency of dosing (q 3–4 h)</td>
</tr>
<tr>
<td>Methadone</td>
<td>Mu agonist, NMDA antagonist</td>
<td>Respiratory depression, constipation, sedation</td>
<td>Ease of dosing (2–3 times daily), half-life facilitates slow taper</td>
<td>Long half-life with unpredictable interpatient variability</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial mu agonist and kappa opioid antagonist</td>
<td>Respiratory depression, constipation, sedation</td>
<td>Long half-life, ease of dosing and taper</td>
<td>Minimal data on use, phase 1 trial formulation contains 30% ethanol</td>
</tr>
</tbody>
</table>

**Second line**

| Phenobarbital | GABA agonist | Sedation, withdrawal seizures | Reduction in hospital stay and daily opioid use | Sedation, impaired suckling |
| Clonidine     | Alpha 2 agonist | Sedation, bradycardia, hypotension, withdrawal hypertension | Reduced symptoms, length of stay in hospital |
| Dexmedetomidine | Alpha 2 agonist | Sedation, bradycardia, hypotension, withdrawal hypertension | 8 times more affinity for alpha 2 receptor than clonidine | Limited data for use in neonates, more studies needed |

**Figure A5: Pharmacologic Management of NAS**
6. Toxicology testing may be done on all known and suspected cases of NAS, defined as follows: * mothers identified by primary or obstetrical caregivers * mothers engaged in high-risk behaviour (i.e. taking street drugs) * mothers identified by child protection agencies or other community agencies * mothers who disclose illicit drug use in pregnancy * mothers who act in an intoxicated manner on admission or during office visits * mothers with a positive history of alcohol and/or drug use/abuse * mothers of newborns presenting with NAS symptoms

Screening in known and suspected cases of NAS is a highly effective way to identify drugs of abuse. Results are critical to guide treatment, diagnose pathophysiology, determine long-term follow-up needs and identify social risks and referrals.

Toxicology testing should supplement maternal self-report, therefore, it may not be needed in cases of maternal disclosure of substance use.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rationale</th>
<th>Implementation Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Toxicology testing may be done on all known and suspected cases of NAS, defined as follows: * mothers identified by primary or obstetrical caregivers * mothers engaged in high-risk behaviour (i.e. taking street drugs) * mothers identified by child protection agencies or other community agencies * mothers who disclose illicit drug use in pregnancy * mothers who act in an intoxicated manner on admission or during office visits * mothers with a positive history of alcohol and/or drug use/abuse * mothers of newborns presenting with NAS symptoms</td>
<td>Screening in known and suspected cases of NAS is a highly effective way to identify drugs of abuse. Results are critical to guide treatment, diagnose pathophysiology, determine long-term follow-up needs and identify social risks and referrals. Toxicology testing should supplement maternal self-report, therefore, it may not be needed in cases of maternal disclosure of substance use.</td>
<td>Diagram B: Algorithm for Assessment and Care of Infants at Risk of NAS are diagram on page 19. Medical directive facilitates early sample collection by nurses. Training for practitioners that includes: physician order, importance of first sample for urine and meconium, collection method and storage of sample, consent requirements. There is no clear opinion regarding consent for testing. Support practitioners to develop a comfort level and confidence in discussing testing matters with women and their support person.</td>
</tr>
</tbody>
</table>

7. Toxicology screening includes the following, but does not limit additional testing deemed necessary by the physician: a) Urine and meconium testing using first sample passed. b) Test urine for cocaine (and its major metabolite benzoylecgonine), methamphetamine, amphetamine, cannabinoids, benzodiazepines, opioid narcotics and benzodiazepines. c) If the urine is positive do not repeat same tests on meconium. Test meconium only for fatty acid ethyl esters (FAEE). d) If urine is negative, test meconium for all substances listed in 2b) and also for FAEE.

Mecamylamine and nicotine hair tests are highly effective in identifying fetal exposure to drugs of abuse since the 2nd trimester. Mecamylamine testing detects longitudinal drug and alcohol use. The infant’s first meconium is best. Collect and store for later analysis when a physician’s order is obtained. Mecamylamine testing must specify the substances to be tested.

The range of substances that meconium is tested for is important, not only to guide current treatment but also long-term treatment, since not all long-term effects may be known at the time of testing. Infants with NAS are at high risk for in-utero exposure to other drugs of abuse and alcohol.

Objective assessment and identification of infants at risk for Fetal Alcohol Spectrum Disorder (FASD) is very important for infants with NAS because women with drug addictions are substantially more likely to consume large amounts of alcohol which is associated with FASD. Mecamylamine analysis of FAGE is a biomarker for heavy maternal drinking. Positive results and the child at high risk (40%) for FASD, a window of opportunity that should not be missed. Positive FAGE calls for neurocognitive follow-up of the child.

**Figure A6: NAS Screening Recommendations**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Purpose</th>
<th>Comparison (Index vs. Reference)</th>
<th>Assessment measure</th>
<th>Primary outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson, 2004 [50]</td>
<td>Double-blind RCT</td>
<td>Efficacy of opioid vs. phenobarbital</td>
<td>Morphine (n = 41) vs. Phenobarbital (n = 34)</td>
<td>Lipitz</td>
<td>Mean length of Rx</td>
<td>8 vs. 12 days* (unadjusted)</td>
</tr>
<tr>
<td>Langenfeld, 2005 [51]</td>
<td>Randomized Trial, Blinding Not Specified</td>
<td>Compare trichrome of opium to oral morphine</td>
<td>Morphine (n = 17) vs. Tincture of Opium (n = 16)</td>
<td>Finnegan</td>
<td>Mean length of Rx</td>
<td>294 vs. 369 days</td>
</tr>
<tr>
<td>Kraft, 2008 [52]</td>
<td>Phase I, Randomized Open Label, Active Control</td>
<td>Feasibility and safety of buprenorphine in Rx of NAS</td>
<td>Buprenorphine (n = 13) vs. Neonatal opioid solution (n = 13)</td>
<td>Modified Finnegan</td>
<td>Mean length of Rx</td>
<td>22 (SD 12) vs. 32 (SD 16) days</td>
</tr>
<tr>
<td>Kraft, 2011 [53]</td>
<td>Phase I, Randomized Open Label, Active Control</td>
<td>Feasibility and safety of buprenorphine</td>
<td>Buprenorphine (n = 12) vs. Neonatal opioid solution (n = 12)</td>
<td>Modified Finnegan</td>
<td>Mean length of Rx</td>
<td>23 vs. 38 days*</td>
</tr>
<tr>
<td>Coyle, 2002 [54]</td>
<td>Partially Randomized, Controlled Trial</td>
<td>Asses whether Rx with DTO + phenobarbital vs. DTO alone is better</td>
<td>Morphine (n = 12) vs. DTO + phenobarbital (n = 13)</td>
<td>Finnegan</td>
<td>Mean length of Rx</td>
<td>23 vs. 42 days</td>
</tr>
<tr>
<td>Agnati, 2009 [55]</td>
<td>Randomized, Double-Blinded Controlled Trial</td>
<td>To assess use of clonidine as an adjunct therapy to opioids to manage NAS</td>
<td>Clonidine (n = 40) vs. Clonidine (n = 40)</td>
<td>Modified Finnegan</td>
<td>Mean length of Rx</td>
<td>11 (95% CI 8.15) vs. 15 (95% CI 12.17) days</td>
</tr>
<tr>
<td>Sun, 2013 [56]</td>
<td>Randomized, Nonblinded Controlled Trial</td>
<td>Clonidine versus phenobarbital to reduce days of Rx with morphine sulfate</td>
<td>Phenobarbital (n = 34) vs. Clonidine (n = 32)</td>
<td>Modified Finnegan</td>
<td>Length of Rx with morphine sulfate</td>
<td>8 – 46 days (95% CI 0.13-0.89)</td>
</tr>
</tbody>
</table>

**Figure A7: Studies of pharmacologic treatment for neonatal abstinence syndrome**

**Abbreviations:** NAS (Neonatal Abstinence Syndrome), Rx (Treatment), # (Number), LOS (Length of Hospital Stay), DTO (Diluted Tincture of Opium).

*indicated p < 0.05.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Natural µ-receptor agonist</td>
<td>0.05–0.2 mg/kg/dose q 3–4 h</td>
<td>No alcohol</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Increase by 0.05 mg/kg</td>
<td></td>
<td>Short half-life (9 h)</td>
<td>Apnea</td>
</tr>
<tr>
<td></td>
<td>Maximum dose: 1.3 mg/kg/day</td>
<td></td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequent dosing</td>
</tr>
<tr>
<td>Methadone</td>
<td>Synthetic complete µ-receptor agonist</td>
<td>0.05–0.1 mg/kg/dose q 12 h, increase</td>
<td>Long half-life (26 h)</td>
<td>Longer duration of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by 0.05 mg/kg q 48 h</td>
<td></td>
<td>Alcohol 8%</td>
</tr>
<tr>
<td></td>
<td>N-methyl-D-aspartate antagonist</td>
<td>Maximum dose: 1 mg/kg/dose²</td>
<td></td>
<td>Frequent follow-up needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Variable half-life)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>γ-amino butyric acid agonist</td>
<td>Loading dose: 16 mg/kg</td>
<td>Long half-life (45–100 h)</td>
<td>Possible hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance dose: 1–4 mg/kg/dose q12 h³</td>
<td></td>
<td>High treatment failure</td>
</tr>
<tr>
<td>Clonidine</td>
<td>α-adrenergic receptor agonist</td>
<td>Initial dose: 0.5–1 µg/kg, followed by</td>
<td>Nonnarcotic antagonist</td>
<td>Alcohol 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5–1.25 µg/kg per dose q 4–6 h⁴</td>
<td></td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No sedation</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No alcohol</td>
<td>Abrupt discontinuation may</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cause rapid rise of blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pressure and heart rate</td>
</tr>
</tbody>
</table>

**Figure A8:** Pharmacologic treatment options for NAS³

**Figure A9:** NAS Pharmacologic Treatment Protocol

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**Morphine**

Morphine is indicated when three consecutive scores are ≥9 according to the Modified Finnegan Scoring System or when the average of two scores or the score for two consecutive intervals is ≥12. If the scores remain ≥8 for 3 consecutive scores or ≥12 on 2 occasions, the morphine dose is increased to the next range i.e. by 0.16 mg/kg/day. If 0.80 mg/kg/day fails to control signs of withdrawal, morphine may be increased to 0.96 to 1.0 mg/kg/day. Clonidine (see below) should be considered at this point.

**Weaning**

Weaning is initiated when scores are <8 for 24 to 48 hours and ordinarily occurs by 10% of the total daily dose with each week occurring no more frequently than every 48 hours to 72 hours. When the total daily dose is <0.2 mg/kg/day, consideration may be given to weaning every 24 hours at the discretion of the physician.

An alternate approach used by some centers is to wean by 0.05 mg/kg/day every 48 to 96 hours as tolerated.

In both approaches, morphine is discontinued when scores are stable for 48 to 72 hours on a dose of 0.05 to 0.1 mg/kg/day.

**Dosing guidelines**

<table>
<thead>
<tr>
<th>Score</th>
<th>Oral Morphine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-10</td>
<td>0.32 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>divided q4-6h</td>
</tr>
<tr>
<td>11-13</td>
<td>0.48 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>divided q4-6h</td>
</tr>
<tr>
<td>14-16</td>
<td>0.64 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>divided q4-6h</td>
</tr>
<tr>
<td>17+</td>
<td>0.80 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>divided q4-6h</td>
</tr>
</tbody>
</table>

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