Neonatal Abstinence Syndrome: A Family Centered Approach

Matthew Grossman, M.D.
Associate Professor of Pediatrics
Yale School of Medicine
Quality and Safety Officer
Yale-New Haven Children’s Hospital
I have no relevant financial relationships to report.
Opioids in the US

- Prescriptions grew 4-fold over last decade
- More deaths than car accidents
  - 91 people die each day from opioids
- In 2012, enough opioids were prescribed to give every adult in the US one prescription


Source: http://familytalk.ca/heroin/
Incidence of NAS in the US, 2000-2016


Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs

Veeral N. Tolia, M.D., Stephen W. Patrick, M.D., M.P.H., Monica M. Bennett, Ph.D., Karna Murthy, M.D., John Sousa, B.S., P. Brian Smith, M.D., M.P.H., M.H.S., Reese H. Clark, M.D., and Alan R. Spitzer, M.D.

ABSTRACT

BACKGROUND
The incidence of the neonatal abstinence syndrome, a drug-withdrawal syndrome that most commonly occurs after in utero exposure to opioids, is known to have
<table>
<thead>
<tr>
<th>SYSTEMS</th>
<th>SIGNS AND SYMPTOMS</th>
<th>SCORE</th>
<th>AM</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>PM</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>DAILY WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL NERVOUS SYSTEM DISTURBANCES</td>
<td>High Pitched Cry</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous High Pitched Cry</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 1 Hour After Feeding</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 2 Hours After Feeding</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperactive Moro Reflex</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Markedly Hyperactive Moro Reflex</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Disturbed</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Disturbed</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Undisturbed</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Undisturbed</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased Muscle Tone</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excoriation (specify area):</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myoclonic Jerks</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generalized Convulsions</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>METABOLIC VASOMOTOR/RESPIRATORY</td>
<td>Sweating</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISTURBANCES</td>
<td>Fever &lt; 101°F (39.3°C)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever &gt; 101°F (39.3°C)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent Yawning (&gt; 3-4 times/interval)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mottling</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal Stuffiness</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sneezing (&gt; 3-4 times/interval)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal Flaring</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory Rate &gt; 60/min</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiration Rate &gt; 60/min with Retractions</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GASTROINTESTINAL DISTURBANCES</td>
<td>Excessive Sucking</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor Feeding</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regurgitation</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Projectile Vomiting</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loose Stools</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Watery Stools</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY**

<table>
<thead>
<tr>
<th></th>
<th>TOTAL SCORE</th>
<th>SCORER'S INITIALS</th>
<th>STATUS OF THERAPY</th>
</tr>
</thead>
</table>

DOSE

Five days old, 5 drops
Two weeks old, 8 drops
Five years old, 25 drops
Adults, 1 Teaspoonful
Source: http://www.projectknow.com

MS Brown et al. Journal of Perinatology 2014; (1-6)
Standard Approach

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
- Staff cares for the baby
Length of Stay: Methadone-Exposed Infants

P < .02
Medication Studies

- **DTO vs. DTO plus clonidine**: 17 days vs. 12 days
- **Morphine vs. Phenobarbitone**: 8 days vs. 12 days
- **Morphine vs. DTO**: 30 days vs. 27 days
- **DTO vs. DTO plus Phenobarbitone**: 79 days vs. 38 days
- **Methadone vs. Morphine**: 17 days vs. 24 days
neonatal withdrawal signs. Clinicians have used discrete or serial scores to assist with therapeutic decisions. The Lipsett tool, also known as the Neonatal Drug Withdrawal Scoring System, was recommended in the 1988 American Academy of Pediatrics publication "Neonatal Drug Withdrawal" probably because it is a relatively simple metric with good sensitivity for identifying clinically important withdrawal. The modified Neonatal Abstinence Scoring System (Fig. 1) is the predominant tool used in the United States. This more comprehensive instrument assigns a cumulative score based on the interval observation of 21 items relating to signs of neonatal withdrawal. In a study administration of this scoring system in infants verified not to have been exposed to prenatal opiate by meconium analysis resulted in a stable median score of 2 during each of the first 3 days of life, with 95th percentile scores of 5.5 and 7 on days 1 and 2, respectively. Infants at risk for NAS should be carefully monitored in the hospital for the development of signs consistent with withdrawal. The appropriate duration of hospital observation is variable and depends on a careful assessment of the maternal drug history. An infant born to a mother on a low-dose prescription opiate with a short half-life (eg, hydrocodone, average half-life, 4 hours) may be safely discharged if there are no signs of withdrawal by 5 days of age, whereas an infant born to a mother on an opiate with a prolonged half-life (eg, morphine) should be observed for a minimum of 5 to 7 days. Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli (both light and sound) by placing the infant in a dark, quiet environment, avoiding stimulation by a familiar baby, and responding quickly to such signs, such as crying, irritability, difficulty sleeping, and feeding difficulties. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and parenteral feeding may be necessary to stabilize the infant's condition in the acute phase and obviate the need for pharmacologic intervention. When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed as long as the infant continues to gain weight. Breastfeeding or the feeding of human milk to the infant has been associated with less severe NAS that presents later and less frequently requires pharmacologic intervention. Methadone is present in very low concentrations in human milk. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01 to 0.13 mg/day in the first 30 days of life and 0.15 to 0.38 mg/day between 30 and 180 days of age. Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term developmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment. Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff should be trained in the correct use of an abstinence assessment tool. In a recent survey of accredited US neonatology fellowship programs, only 55% had implemented a written NAS protocol, and only 68% used a published abstinence scoring system. RATIONALE AND COMPARATIVE EVIDENCE FOR PHARMACOLOGIC TREATMENT

Drug therapy is indicated to relieve moderate to severe signs of NAS and to prevent complications such as fever, weight loss, and seizures if an infant does not respond to a committed program of nonpharmacologic support. Since the introduction of the abstinence scores in 1975, published reports have documented that the decision to initiate pharmacologic treatment has been based on single or serial withdrawal scores. However, no studies to date have compared the use of different withdrawal score thresholds for initiating pharmacologic intervention on short-term outcomes (eg, severity and duration of withdrawal signs, weight gain, duration of hospitalization, need for pharmacologic treatment, or cumulative drug exposure). Withdrawal from opioids or sedative-hypnotic drugs may be life threatening, but ultimately, drug withdrawal is a self-limited process. Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs. Studies have not addressed whether long-term morbidity related to neonatal drug withdrawal is decreased by pharmacologic management of affected infants, or whether continued postnatal drug exposure augments the risk of neurobehavioral and other morbidities. It is possible that pharmacologic therapy of the infant may introduce or reinforce a maternal disposition to rely on drugs for the treatment of infant discomfort or crying behavior.

Clinicians have treated NAS with a variety of drug preparations, including opioids (butorphanol, opium, and paregoric), barbiturates (phenobarbital), benzodiazepines (diazepam, lorazepam), and phenothiazines (chlorpromazine). Information pertinent to the use of these drug preparations in infants is wellsummarized in the previous American Academy of Pediatrics statement. Recent surveys have documented that, in accord with the recommendations of that statement, 84% of UK and 85% of US clinicians use an opioid (morphine or meperidine) as the drug of first choice. The majority of practitioners use meperidine as a second drug if the opiate does not adequately control withdrawal signs. Daily doses of morphine ranges from 0.24 to 0.6 mg/kg per day to 1.5 mg/kg per day. Paregoric is no longer used, because it contains volatile concentrations of other opioids, as well as toxic ingredients such as ammonia, anisate, alcohol, and boric acid. The use of diazepam has also fallen into disfavor because of a documented lack of efficacy compared with other agents and because of its adverse effects or infant sleep and awake reflexes.
adopting appropriate infant positioning and comforting techniques (swaying, rocking), and providing frequent small volumes of hyperaliment formula or human milk to minimize hunger and allow for adequate growth. Gastric needs may be as high as 150 to 250 cal/kg per day because of increased energy expenditure and loss of calories from regression, vomiting, and/or loose stools.\textsuperscript{10,12} The infant needs to be carefully observed to recognize fever, dehydration, or weight loss promptly. The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment. Maternal screening for comorbidities, such as HIV or hepatitis C virus infections and poydrug abuse, needs to be performed. Additional supportive care in the form of intravenous fluids, replacement electrolytes, and soiling free feedings may be necessary to stabilize the infant's condition in the acute phase and obviate the need for pharmacologic intervention. When possible, and if not otherwise contraindicated, mothers who adhere to a supervised drug treatment program should be encouraged to breastfeed as long as the infant continues to gain weight. Breastfeeding or the feeding of human milk has been associated with less severe NAS that presents later and therefore requires pharmacologic intervention.\textsuperscript{10,12}

Methadone is present in very low concentrations in human milk. Cumulative daily intake of methadone in fully breastfed infants has been estimated to range from 0.01 to 0.15 mg/day in the first 30 days of life\textsuperscript{13,14} and 0.15 to 0.30 mg/day between 30 and 180 days of age.\textsuperscript{15,16} Similarly, the amount of buprenorphine excreted in human milk is small. Although more information is needed to evaluate long-term neurodevelopmental outcome of infants exposed to small quantities of buprenorphine, there is no clear reason to discourage breastfeeding in mothers who adhere to methadone or buprenorphine maintenance treatment.\textsuperscript{11,12}

Each nursery should adopt a protocol for the evaluation and management of neonatal withdrawal, and staff should be trained in the correct use of an appropriate assessment tool. In a recent survey of accredited US neonatology fellowship programs, only 56% had implemented a written NAS protocol, and only 6% used a published abstinence scoring system.\textsuperscript{102}

RATIONAL AND COMPARATIVE EVIDENCE FOR PHARMACOLOGIC TREATMENT

Drug treatment is indicated to relieve moderate to severe signs of NAS and to prevent complications such as fever, weight loss, and seizures if an infant does not respond to a committed program of nonpharmacologic support. Since the introduction of the abstinence scales in 1975, published reports have documented that the decision to initiate pharmacologic treatment has been based on single or serial withdrawal scores. However, no studies to date have compared the use of different withdrawal score thresholds for initiating pharmacologic intervention on short-term outcomes (e.g., severity and duration of withdrawal signs) with the effect of treatment.\textsuperscript{12,13} Daily scores of morphine range from 0.34 to 0.49 mg/kg per day.\textsuperscript{12,13} Daily scores of morphine range from 0.34 to 0.49 mg/kg per day.\textsuperscript{12,13}

Although buprenorphine was compared with a control treatment that could include a nonpharmacologic intervention, a placebo treatment, or another opioid and/or sedative drug. The authors prospectively designated 4 primary outcomes (failure of treatment to control withdrawal signs, incidence of seizures, survival, and neurodevelopmental outcome) for meta-analysis. Treatment failure was defined variably as either the inability of the treatment to maintain abstinence scores within a preset “safe” level or the need to add another drug treatment. Some studies did not report primary outcomes and included quantified secondary outcomes (e.g., duration of treatment, duration of hospitalization, rate of weight gain, etc.).

Seven studies of opioid treatment that enrolled a total of 398 infants were identified between 1983 and 2004.\textsuperscript{13} Methodologic flaws were common and included random patient allocation; substantial and often unexplained differences in allocation of patients to treatment groups; imbalances in group characteristics after randomization; failure to mask study treatments; and failure to mask outcome measurements. In the single study that assessed oral morphine treatment versus supportive therapy only, 3 consecutive Finnegan scores >8 prompted institution of the intervention.\textsuperscript{13} No significant effect of morphine was found on the rate of treatment failure. Oral morphine significantly increased the duration of hospitalization and the length of hospital stay, but it did not reduce the number of days required to regain weight and duration of supportive care. Four studies compared treatment failure rates of opioids (buprenorphine, oral morphine, or methadone with phenobarbital).\textsuperscript{10,12,13} Neither the meta-analysis nor any individual study identified a significant difference in treatment failure. One study reported a lower incidence of seizures in the opioid (paracetamol) treatment group.\textsuperscript{13} No consistent trends in secondary outcomes were observed, although 1 study reported a shorter duration of therapy in the phenobarbitone compared with the paracetamol treatment group.\textsuperscript{13} and another underreported or observed the episodes when the opioid was oral morphine.\textsuperscript{13} Three studies individually and in combination reported significantly lower rates of treatment failure in infants assigned to opioid (paracetamol or methadone) with phenobarbitone compared with dexamethasone therapy.\textsuperscript{10,12,13} but did not define differences in secondary outcomes. No studies reported mortality or neurodevelopmental outcomes.

A second Cochrane review analyzed 6 trials involving 305 infants published between 1998 and 2002 in which adjuvant treatment of NAS was compared with a nonopiod therapy. Methodologic concerns were similar to the opioid treatment trials. In the sole study of phenobarbitone versus supportive care, no difference in treatment failure was found, but treatment significantly increased the duration of therapy and hospital stay.\textsuperscript{13} A small study that allocated infants already treated with alute, a mixture of opium (GTO) to phenobarbitone as a second drug versus no additional treatment identified no infants in either group with treatment failure but observed significant reductions in the duration of hospitalization (58 to 76 days) and the maximal daily dose of opium in the phenobarbitone-treated infants.\textsuperscript{12} Infants were discharged from the hospital once they were no longer taking opioids. However, the mean duration of phenobarbitone treatment was 3.5 months. If 3 studies of patients treated with phenobarbitone and dexamethasone, treatment found a significantly lower rate of treatment failure in phenobarbitone.\textsuperscript{12,13} One study of phenobarbitone versus ciprofloxacin found no differences in primary or secondary outcomes.

Since 2004, a number of small studies of varying methodologic quality have compared pharmacologic treatments in a prospective randomized double-blind study. Langenfeld et al.\textsuperscript{12} could not identify differences in duration of treatment, duration of hospitalization, or in weight gain (g/day) in infants treated with either DOD or oral morphine treatments. A retrospective study found no difference in length of hospitalization in infants with NAS who were treated with methadone or oral morphine solution, but did correlate higher maternal methadone doses with longer lengths of stay.\textsuperscript{127} Ehrer et al.\textsuperscript{128} examined the incidence of NAS in infants born to mothers maintained with methadone, morphine, or buprenorphine and compared pheno- barbitone and oral morphine treatments in affected infants. Sixty-eight percent of infants born to mothers maintained on methadone required pharmacologic treatment at a mean age of 58 hours, compared with 82% of infants born at a mean age of 33 hours in the morphine group and 21% of infants at a mean age of 54 hours in the buprenorphine group. The duration of treatment was significantly shorter for infants who received morphine compared with infants who were treated with phenobarbitone. A randomized, controlled trial of sublingual buprenorphine versus maternal opioid solution for the treatment of NAS showed a non-significant reduction in length of treatment and duration of hospitalization in the buprenorphine group.\textsuperscript{82} Buprenorphine therapy was well tolerated.

Comedone is an adrenergic receptor agonist that has been used in combination with an opioid or other drug in older children and adults to reduce withdrawal symptoms.\textsuperscript{18} A negative feedback mechanism, comedone...
OUTCOME
Assessment of potential long-term morbidity specifically attributable to neonatal opioid withdrawal and its treatment is difficult to evaluate. Few studies have followed drug-exposed children beyond the first few years of life. Confounding variables, such as environmental and developmental influences, complicate the interpretation of outcomes. In a small study, developmental scores on the Bayley Scales of Infant Development were not affected by the severity of withdrawal or the treatment chosen. Mean scores on the Bayley Scales of Infant Development were similar for all infants treated for withdrawal, including those receiving pharmaceutical agents or a combination therapy. Scores of infants whose withdrawal was moderate to severe were comparable to normal infants who had been treated with a combination of clonidine and chloral hydrate than children treated with a combination of clonidine and chloral hydrate or a combination of clonidine and chloral hydrate.

MANAGEMENT OF ACQUIRED OPIOID AND BENZODIAZEPINE DEPENDENCY
One of the cornerstone treatments for neonatal opioid addiction is the use of methadone or buprenorphine. Methadone is a long-acting opioid agonist that is effective for the management of opioid withdrawal in neonates. However, the use of methadone in neonates is associated with significant side effects, including respiratory depression, sedation, and feeding difficulties. Buprenorphine is a partial opioid agonist that is effective in the management of opioid withdrawal in neonates. However, the use of buprenorphine in neonates is associated with significant side effects, including respiratory depression, sedation, and feeding difficulties.

A recent study evaluated the efficacy of methadone and buprenorphine in the management of opioid withdrawal in neonates. The study found that methadone was more effective than buprenorphine in the management of opioid withdrawal in neonates. However, the use of methadone in neonates is associated with significant side effects, including respiratory depression, sedation, and feeding difficulties. Buprenorphine is a partial opioid agonist that is effective in the management of opioid withdrawal in neonates. However, the use of buprenorphine in neonates is associated with significant side effects, including respiratory depression, sedation, and feeding difficulties.

70% sensitivity and 79% specificity and that an infusion duration of 24 hours was 96% sensitive and 51% specific for withdrawal. In adults, concomitant treatment with non-opioid-based agents is often necessary to reduce the likelihood of withdrawal. Signs and symptoms of withdrawal from the benzodiazepine can occur within 24 hours of cessation of therapy. The refinement of pain management in children over the past 2 decades has witnessed an expansion of the use of opioids in the intensive care setting. As a result, more children have been treated for opiate or opiate withdrawal symptoms as a common cause of hospitalization. Fentanyl, a pure μ-opioid receptor agonist, has become the opioid of choice because of its rapid onset of action, short duration of effect, and lack of cross-tolerance. Opioid therapy is an even more powerful tool in the management of opioid withdrawal. Fentanyl is a pure μ-opioid receptor agonist that is effective in the management of opioid withdrawal in neonates. However, the use of fentanyl in neonates is associated with significant side effects, including respiratory depression, sedation, and feeding difficulties.

Kote et al. reported that among 28 mechanically ventilated children aged 1 week to 2 months (mean, 6 months) who were treated for 24 hours with a continuous fentanyl infusion, 13 of 25 children (52%) developed withdrawal defined as a Finnegan score >8. In this study, a cumulative fentanyl exposure of 4.1 mg/kg or 9 days of therapy was 100% predictive of withdrawal. Recently, in a prospective study of 18 neonates treated with fentanyl for a minimum of 24 hours, Demougeot et al. reported that a cumulative fentanyl dose >15 μg/kg predicted withdrawal with 70% sensitivity and 79% specificity and that an infusion duration of 24 hours was 96% sensitive and 51% specific for withdrawal.
Percent of NAS Patients Treated with Morphine

Year

% Treated with Morphine

2003 2004 2005 2006 2007 2008 2009 2010
Length of Stay: Methadone exposed infants

Mean = 22.5

LENGTH OF STAY (Days)

LCL: 0.0
UCL: 47.1

ADMIT DATE
The standard approach: why?

- Medications
Intervention 1

Focus on non-pharmacologic care
Length of Stay: Methadone exposed infants

Mean = 22.5
Mean = 13.2

Standardized non-pharm care
The standard approach: why?

- Medications
- NICU
Intervention 2

Direct transfer to the general inpatient unit
Length of Stay: Methadone exposed infants

- Mean = 10.2
- Mean = 13.2
- Mean = 22.5

Direct transfer to inpatient unit
Standardized non-pharm care

LENGTH OF STAY (Days)
ADMIT DATE
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
<table>
<thead>
<tr>
<th>SYSTEMS</th>
<th>SIGNS AND SYMPTOMS</th>
<th>SCORE</th>
<th>AM</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>PM</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>DAILY WT.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Pitched Cry</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous High Pitched Cry</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 1 Hour After Feeding</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 2 Hours After Feeding</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperactive Moro Reflex</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Markedly Hyperactive Moro Reflex</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Disturbed</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Disturbed</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild Tremors Undisturbed</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate Severe Tremors Undisturbed</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased Muscle Tone</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excoriation (specify area):</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myoclonic Jerks</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generalized Convulsions</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Sweating</strong></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever &lt; 101°F (39.3°C)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever &gt; 101°F (39.3°C)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent Yawning (&gt; 3-4 times/interval)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mottling</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal Stuffiness</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sneezing (&gt; 3-4 times/interval)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal Flaring</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory Rate &gt; 60/min</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiration Rate &gt; 60/min with Retractions</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Excessive Sucking</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor Feeding</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regurgitation</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Projectile Vomiting</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loose Stools</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Watery Stools</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY**

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>SCORER'S INITIALS</th>
<th>STATUS OF THERAPY</th>
</tr>
</thead>
</table>

“The infant with a score of “7” or less was not treated with drugs for the abstinence syndrome because, in our experience, he would recover rapidly with swaddling and demand feedings. Infants whose score was “8” or above were treated pharmacologically”

Problems with the Finnegan

- Long lengths of stay and lots of meds
- Purpose of treatment is to get the scores below threshold
- Must disturb the infant and exacerbate signs of withdrawal
- Can be slow to respond
- Powerful and potentially harmful meds to give to treat a sneeze or a yawn
Intervention 3

Discontinuation of the Finnegan Scoring tool and adoption of a functional scoring approach
1) Can the baby eat?
2) Can the baby sleep?
3) Can the baby be consoled?
• Analyzed 50 consecutive NAS babies admitted to our general inpatient unit from March 2014 to August 2015

• Assessed every 2-6 hours using the FNASS, but did not guide management

• Management decisions based on ESC
Outcomes

1. Proportion of infants treated with morphine vs. proportion predicted to be treated with morphine using the FNASS approach
2. Days the two approaches disagreed
3. FNASS scores the day after the two approaches disagreed
Results

Proportion of Infants that Received Morphine

- Received Morphine (ESC): 12%
- Would Have Received Morphine (Finnegan): 62%

p < .001

NAS infants (n=50)
Results

• On 78 days (26.4%) the ESC Led to LESS Morphine than Predicted by The Finnegan
  • The following day, the average Finnegan score decreased by 0.9 points, and decreased in 69% of cases.

• On 2 days (0.7%) the ESC Led to MORE Morphine than Predicted by The Finnegan
  • In both cases the average Finnegan score increased by 1.7 Points the next day
Results

- No readmissions
- No seizures
- No ICU transfers
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
Intervention 4

Decrease in morphine up to 3 times per day
Intervention 5

PRN Dosing
Length of Stay: Methadone exposed infants

- Standardized non-pharm care
- Direct transfer to inpatient unit
- Spread to NICU team
- Novel assessment tool on inpatient unit
- Prenatal counseling
- Rapid med weaning

Length of Stay: Mean=22.5
Mean=13.2
Mean=10.2
Mean=7.7

ADMIT DATE
LENGTH OF STAY (Days)
The standard approach: why?

- Medications
- NICU
- Finnegan Scores
- Medication Dosing
- Staff cares for the baby
How do moms feel?

- Addiction is misunderstood
- Guilty
- Judged
- Mistrusting of nurses
“His nurse was like ‘his muscles are locking up because of his junkie mom’. I didn’t want to visit, I would call before and if that nurse was there, I wouldn’t even go.
“...because we’re gonna leave and he’s gonna cry and they’re gonna leave him crying because they’re gonna be like, ‘you know what? His parents are jerks!’”
if you’re using while you’re pregnant, you have a problem; a big problem . . . and you need help. You obviously don’t care about your-self, about anything, except the drug. Make it a little bit easier on that mother if she’s showing initiative . . . if she’s taking the time to be there. If she loves her child, you can see it and you can feel it. If it’s obvious that she’s there for the baby then embrace it; make it easier. You don’t know what her circumstances are. You don’t know what she’s been through or how hard her life has been. You don’t know what she was feeling when she was pregnant . . . if she was being abused, if she was poor. Whatever the reason she was using while she was pregnant . . . you just don’t know. So, try to make it easier for her.
Intervention 6

Empowering messaging
Old Protocol

- Goal: suppress withdrawal signs
- NICU: Mom visits
- Finnegan Scores: treat the number
- “supportive care”
- “feed on demand”
- Morphine
- Surprise!
- Staff takes care of infant

New Protocol

- Goal: have infant function as a normal neonate
- Mother and child together
- Eat/Sleep/Console: treat the infant
- SUPPORTIVE CARE
- No feeding schedule
- Meds on page 3
- Prenatal preparation
- Staff coaches parents
Length of Stay: Methadone exposed infants

- Standardized non-pharm care
  - Mean=22.5
- Direct transfer to inpatient unit
  - Mean=13.2
- Novel assessment tool on inpatient unit
  - Mean=10.2
- Spread to NICU team
- Prenatal counseling
  - Mean=7.7
- Rapid med weaning
  - Meds as needed
- Empowering messaging
  - Mean=5.9

Length of Stay: Methadone exposed infants

Mean values for different interventions.
Average Length of Stay - Methadone Exposed Infants

- Protocol Change: More aggressive weans
- Discontinued Finnegan Scoring
- Transfers directly from WBN to Floor
- Focus on supportive management
- NICU included in effort
- More aggressive weans

Year: 2003 to 2016
Average Length of Stay (Days): 0 to 35
Length of Stay (days): Methadone Exposed Infants
Percent Treated with Morphine

Date

Percent Treated


0.0% 10.0% 20.0% 30.0% 40.0% 50.0% 60.0% 70.0% 80.0% 90.0% 100.0%
Average Maximum Morphine Dose

Average maximum morphine dose (mg/dose) vs. Year


Average maximum morphine dose (mg/dose) decreases over time with a p-value of < .001.
Breastfeeding Rate

% Breastfeeding

Year

Total Average Cost of NAS Care

Year: 2003 to 2015

Total Cost ($): $0 to $60,000

p < .001
Other ESC references


Additional Spread
Long-Term Outcomes
Conclusions

- Hugs before drugs
  - Empower families
  - Rooming-in
  - Non-Pharmacologic care as 1\textsuperscript{st} line treatment
  - ESC approach
  - PRN meds

- 3 Keys to treatment
  - Mom is antibiotics
  - Pretend it is a baby
  - Treat the mom like a mom

- Ask why

Source: Grossman Family Album
Acknowledgements

- David Hersh, MD
- Adam Berkwitt, MD
- Erin Nozet, MD
- Marcelle Applewaite, RN
- Kim Carter, RN
- Liz O’Mara, RN
- Matt Bizzarro, MD
- Yogangi Malhotra, MD
- Jonathan Miller, MD
- Camisha Taylor, RN
- Rachel Osborn, MD