NEONATAL ABSTINENCE SYNDROME

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Disclosures

- I have no financial disclosures to discuss
Neonatal Abstinence Syndrome

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The neonatal abstinence syndrome was first described in the literature in the 1970s by Dr. Loretta Finnegar. Although this syndrome has been recognized for more than four decades, there have been substantial changes in the past 10 years, including a dramatic increase in prevalence and changes in both the exposure substance and clinical management. There has also been a considerable amount of research on the neonatal abstinence syndrome, and effective management strategies have been developed. However, gaps still exist, including a lack of clarity and consistency in how the syndrome is defined, measured, and managed. In addition, much of the research has focused on the infant in isolation from the mother, and many hospitals lack protocols to guide treatment. The purpose of this review is to summarize the current literature on the neonatal abstinence syndrome, including clinical characteristics, prevention, identification, and treatment. Approaches to care that recognize the importance of the infant-mother dyad are emphasized when possible.

Epidemiology

The incidence of the neonatal abstinence syndrome has increased substantially in the past decade. In 2012, the syndrome was diagnosed in 21,732 infants in the United States, which represents a sevenfold increase in the prevalence of the neonatal abstinence syndrome in other locations, including England, Canada, and Western Australia, and reflects an increasing global problem. The increase in cases of the neonatal abstinence syndrome is attributed to the increased use of opioid substances and the increased use of prescribed opioids for pain control in pregnant women, which is attributed to the increased use of prescribed opioids for pain control and the increased use of prescribed opioids for pain control in pregnant women.
Objectives

- Discuss the history of Neonatal Abstinence Syndrome in the United States
- Review the incidence and etiology of NAS in the United States
- Discuss effects of various drugs on developing infants
- Identify symptoms of NAS, and apply common scoring systems to correctly manage treatment
- Discuss treatment options for infants with NAS
Definition

“...a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy.” (Pediatrics, Kocherlakota, Aug 2014, Vol 134, Issue 2)

“...a postnatal opioid withdrawal syndrome that can occur in 55 to 94% of newborns whose mothers were addicted to or treated with opioids while pregnant.” (NEJM, 2016; 375: 2468-2479)
History

- Opium is made from the collected fluid of unripe poppy seed pods, air dried, and rolled into balls
- Historically, opium use can be traced to Mesopotamia, circa 3400 BC
- Morphine first isolated in 1804 by Friedrich Sertturner. After the Civil War, addiction came to the attention to medical society of the U.S.
- Heroin first synthesized in 1874, initially a “non-addictive” morphine substitute
- Then, banned by the Heroin Act in 1924
- 2000 tons of opium are legally grown annually, in Australia, India and Turkey. This provides the world’s legal opiates
The first neonate with withdrawal symptoms was described by Menninger-Lerchenthal, in 1875. The diagnosis was congenital morphinism.

Sparse further case studies were reported, but no treatments until ...


Still, congenital morphinism remained obscure until 1947, when another case report was made of an infant with seizures that was successfully treated (Perlstein, JAMA 1947; 135(10) 633)
Around this time, OB/GYN and Pediatricians became more aware of the problem.

Rosenthal, et al, 1964: “reports of cases from the beginning of the century ... point to the fact that infants born to opiate or opiate-like drug-addicted (at time of delivery) mothers may be addicted.”

Methadone was introduced that year, and initially thought safe for pregnant mothers.

Buprenorphine introduced in 2002 to the US, and also thought a better alternative to methadone.
“... a postnatal opioid withdrawal syndrome that can occur in 55 to 94% of newborns whose mothers were addicted to or treated with opioids while pregnant.” (NEJM, 2016; 375: 2468-2479)

With time, other substances are known to cause similar clinical withdrawal symptoms in infants

- SSRIs
- Amphetamines
- Other illicit drugs (marijuana, cocaine)
- Benzodiazepines
- TCA’s
United States Epidemiology

- Kids Inpatient Database (2012): 5.8/1000 hospital births, up from 1/2/1000 in 2000
- State Inpatient Databases of the Healthcare Cost and Utilization Project: 1.5/1000 births in 1999, up to 6/1000 in 2013
- Tolia et al, NEJM, 2015: 27/1000 admissions, among 299 NICU’s surveyed
- The treatment rate of infants exposed to intrauterine opioids range from 42-94%
- One study found that 6% of mothers used opiates for greater than one month during pregnancy
- 1.8% use antidepressants
- 3% use benzodiazepines
Financial Burden

- In 2012, 16,007 people died from opioid analgesics, 5,925 involved heroin.
- The Tennessian in 2014: “The average cost to deliver a drug-dependent baby is $62,000 compared to $4,700 for a health child.”
- In 2010-11, Indiana ranked 5th in the nation for opiate abuse rates: 5.68% of population. The national average is 4.6%.
- Cost to Indiana was $887 million (2010-22) in opiate-abuse related care.
- In 2012, KY had 2nd highest age-adjusted drug poisoning deaths in US: 25/100,000.
Pathophysiology

- As of yet, no clear etiology has been found to explain opiate withdrawal
- Opiates can easily cross the placenta; cocaine or heroin use can increase the opiate dose delivered to the fetus
- Developing brain tissues higher in Mu-receptors, compared to adults
Maternal Screening

- Reassure mother that medically screening is not a legal process
- Consider screening mothers who:
  - History of drug use within the last year
  - History of narcotic use
  - History of prior drug use during pregnancy
  - Those with minimal prenatal care
Infant Screening

- Screen all infants with a positive maternal history/screen
- First void urine or meconium is preferred
- May send umbilical cord blood
- False positives:
  - Meconium mixed with alcohol used to clean sample site
  - Maternal analgesia
- False negatives:
  - Unable to get first void
  - Improper storage/handling of sample
  - Synthetic or designer drugs may not show on routine screens
Choose sample based on duration of use

- Urine easiest, but only detects drug use from the preceding several days
- Meconium most sensitive for opiates and cocaine, can detect from 20 weeks gestation
- Hair and umbilical cord can be sensitive, but often delayed due to send-out labs
- Neonatal hair can be as sensitive as meconium for opiates, but less for cocaine and cannabis. Also, can only be used to detect 3rd trimester drug use
Symptoms

- Neurologic
  - Excessive irritability
  - Hyper reflexive
  - Decreased sleep
  - Increased muscle tone
  - Tremors
  - Myoclonic jerks
  - Seizures

- Gastrointestinal
  - Diarrhea
  - Regurgitation
  - Poor suckling

- Autonomic
  - Diaphoresis
  - Temperature instability
  - Sneezing
  - Mottling
Symptom Onset

- Onset and duration vary based on the half-life of the substance
- Heroin: typically first 24-48 hours of life
- Morphine/Buprenorphine: 36 hours
- Methadone: 60 hours; symptoms may present out to 4 weeks post delivery!
- Seizures may occur in 2-11% of NAS infants, and may need an EEG to differentiate from hyperactivity
SSRIs
- Generally onset in 48 hours; in 1 study by Levinson-Castiel et al (2004), all had symptoms by 4 days of life. Their study, paroxetine < 20mg/day was safest
- High pitched cry, increased tone, poor sleep
- Up to 1/3 of infants

Stimulants
- Relatively little data about prescription amphetamines, methamphetamine, or ecstasy
- Methamphetamine linked to lower birth weight; lack of energy and lower arousal from sleep
- Long term data lacking
- Tobacco
  - More excitable, increased tone, more signs of CNS distress
  - Potentially long term effects from low birth rates and lower IQ
- Marijuana
  - Mild withdrawal symptoms, poor autonomic control, though this seems to normalize by 1 year
  - Increased risks of developmental problems, more depressive symptoms
Cocaine

- Estimated 2 million Americans were pre-natally exposed to cocaine
- Estimated that 50,000 children born annually are exposed to cocaine
- Higher sensory/motor asymmetry, decreased tone, jitteriness

- In first year, impaired visual speed. Later, have decreased attention and higher impulsivity and aggressive behavior
Classifying withdrawal symptoms

- Numerous scales exist, in attempts to standardize symptom reporting and treatment algorithms
  - Finnegan - 31 data points, every 4 hours
  - Lipsitz - Recommended by AAP in 1998. Similar, but simpler, than Finnegan
  - Neonatal Withdrawal Inventory - 8 point checklist, 7 symptoms. Treat if score > 8
  - Neonatal Narcotic Withdrawal Index - 6 signs with an “other” category of 12 more signs. Score 0-2 per item, treat if > 5
  - Ostrea tool - 6 items to score, no correlation of score with treatment, thus not used often clinically
Finnegan NAS tool

- Introduced in 1975 by Dr. Loretta P Finnegan, while working as a pediatrician in Philadelphia General Hospital
- Initially designed to document opiate (specifically, heroin) withdrawal
- Modified/simplified version released in 2013
- Most commonly used scale in the US
<table>
<thead>
<tr>
<th>System</th>
<th>Signs and Symptoms</th>
<th>Score</th>
<th>AM</th>
<th>PM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td>Excessive high-pitched (or other) cry &lt;5 mins</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<td>Continuous high-pitched (or other) cry &gt;5 mins</td>
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<td></td>
<td>Sleeps &lt;1 hour after feeding</td>
<td>3</td>
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<tr>
<td></td>
<td>Sleeps &lt;2 hours after feeding</td>
<td>2</td>
<td></td>
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<td></td>
<td>Sleeps &lt;3 hours after feeding</td>
<td>1</td>
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<td></td>
<td>Hyperactive Moro reflex</td>
<td>2</td>
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<td></td>
<td>Markedly hyperactive Moro reflex</td>
<td>3</td>
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<tr>
<td></td>
<td>Mild tremors when disturbed</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>Moderate-severe tremors when disturbed</td>
<td>2</td>
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<tr>
<td></td>
<td>Mild tremors when undisturbed</td>
<td>3</td>
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<tr>
<td></td>
<td>Moderate-severe tremors when undisturbed</td>
<td>4</td>
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<td></td>
<td>Increased muscle tone</td>
<td>1</td>
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<td></td>
<td>Excoriation (chin, knees, elbow, toes, nose)</td>
<td>1</td>
<td></td>
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<td></td>
<td>Myotonic jerks (twisting/jerking of limbs)</td>
<td>3</td>
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<td></td>
<td>Generalized convulsions</td>
<td>5</td>
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<tr>
<td>Metabolic/Vascular</td>
<td>Swallowing</td>
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<tr>
<td>Respiratory Disturbances</td>
<td>Hyperthermia 99.90-100.94° F</td>
<td>1</td>
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<td></td>
<td>Hyperthermia &gt;101.32° F</td>
<td>2</td>
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<td></td>
<td>Frequent yawning (&gt;3-4 times/scoring interval)</td>
<td>1</td>
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<tr>
<td></td>
<td>Mottling</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>Nasal stuffiness</td>
<td>1</td>
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<td>Shreoning (&gt;3-4 times/scoring interval)</td>
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<td></td>
<td>Nasal flaring</td>
<td>2</td>
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<td></td>
<td>Respiratory rate &gt;60/min</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory rate &gt;60/min with retections</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal Disturbances</td>
<td>Excessive sucking</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>Poor feeding (infrequent/uncoordinated bark)</td>
<td>2</td>
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<td></td>
<td>Regurgitation (22 times during past feeding)</td>
<td>2</td>
<td></td>
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<td></td>
<td>Projectile vomiting</td>
<td>3</td>
<td></td>
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<tr>
<td></td>
<td>Loose stools (curdly/berry appearance)</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>Watery stools (water ring on diaper around stool)</td>
<td>3</td>
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<td></td>
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<tr>
<td>Total Score</td>
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<td>Date/Time</td>
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<tr>
<td>Initials of Scorer</td>
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</table>
Finnegan Scoring

- Begin at 2 hours of life, then no more than every 4 hours
- Screening interval shortens to hourly if a score is > 8
- “24 Rule.” 3 consecutive scores > 8, or 2 scores > 12
- Decision to treat is clinical, taking into account the myriad of symptoms, particularly respiratory and known maternal exposure
- Treatment doses based on NAS scores
TABLE 4. Neonatal Drug-Withdrawal Scoring System

<table>
<thead>
<tr>
<th>Signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Tremors (muscle activity of limbs)</td>
<td>Normal</td>
</tr>
<tr>
<td>Irritability (excessive crying)</td>
<td>None</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
</tr>
<tr>
<td>Stools</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
</tr>
<tr>
<td>Skin abrasions</td>
<td>No</td>
</tr>
<tr>
<td>Respiratory rate/minute</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Repetitive sneezing</td>
<td>No</td>
</tr>
<tr>
<td>Repetitive yawning</td>
<td>No</td>
</tr>
<tr>
<td>Vomiting</td>
<td>No</td>
</tr>
<tr>
<td>Fever</td>
<td>No</td>
</tr>
</tbody>
</table>

Non Pharmacologic Treatments

- Soothing techniques: swaddling, pacifier, rocking
- Environmental modification (quiet, dark rooms)
- Maternal education and reassurance
  - Babies cry for numerous reasons
  - Maternal guilt over infant’s condition
  - Psychiatric or rehab services for mother
- 60-80% of infant won’t respond, and end up needing pharmacotherapy
Increased metabolic activity may increase infant caloric needs, up to 150 calories/kg/day
  ▶ However, many of these infants have concurrent feeding difficulties, such as regurgitation and emesis

Hyperthermia can be confused with fever/sepsis

Skin excoriation is common, both from copious watery diarrhea, as well as rubbing/writhing. Often requires use of barrier creams
Pharmacotherapy

- Goal: relief of signs, such as seizures, fever, weight loss, sufficient to allow parental care of infant
- No national standardized guidelines
- Treatment options vary depending on maternal drug exposure
- Typically, opiates used for opioid-exposed infants
- May use 2nd line agents as needed
- May consider other treatment options if polypharmacy/polysubstance use
Opiate Biochemistry

- Opioids are derived from opiates, which are derived from opium
  - Prototypic (derived from opium, eg morphine and codeine)
  - Semisynthetic (heroin, oxycodone)
  - Fully synthetic (methadone, fentanyl)

- Opioid receptors:
  - Mu: Triggers brain reward system, linked with analgesia and addiction, Main site of action of morphine and opiates
  - Kappa: Analgesia, with dysphoria, diuresis. Possible antagonist target to treat depression
  - Delta: modulate pain transmission, nociception and hyperalgesia
Mu receptors more common in infants

Locus coeruleus in the pons is sensitive to opiates - increases norepinephrine production upon withdrawal of opiate

Dorsal raphe nucleus decreased 5-HT production, leading to sleep disturbances
Treatment of opiate-exposed infants

- Several options, including morphine, dilute tincture of opium, methadone
- Typically use morphine sulfate (0.4mg/ml)
  - Fully mu opioid agonist
  - Short duration of action
  - Relatively safe, allows dose titration
- Morphine hydrochloride, 0.2mg/ml, can be used
- DTO: contains 1.9% alcohol, is falling out of favor
Dosing

- Typically for Finnegan score of 9-12, start at 0.04mg morphine and titrate up
- Titrate dose up until the scores are under 8
- Maintain this dose for 48 hours, then try to wean by 0.02mg every 24 hours
  - May need to increase dose and re-titrates for symptom relapse
Methadone

- FDA approved alternative to morphine
- Fully synthetic mu-opioid receptor drug
  - Half life of 25-32 hours, leading to more “basal” levels of opiate and less frequent (BID) dosing
  - However, takes longer to wean, and can lead to drug “stacking”
  - Some formulations contain alcohol
- Accumulates in adipose disuse; this may explain why withdrawal symptoms less severe
- DTO, morphine, and methadone proven equivalent therapeutically
Additional treatment options?

- Mother-NAS trial, looked at methadone vs buprenorphine
- Subutex used instead of suboxone to avoid confounding with naloxone
- Infants born to mothers on subutex had:
  - shorter hospital stays (10 vs 17.5 hospital days)
  - Lower treatment doses of morphine (1.1mg, vs 10.4mg)
  - Shorter treatment days (4.1 vs 9.9)
- As of November 2015, only methadone is FDA approved for treatment of opioid dependence in pregnant women ... but should we change these women over to subutex?
Buprenorphine

- Partial mu-opioid agonist
- Not often used for NAS, little data
- 1 trial, from Kraft et al, compared SL buprenorphine to oral opium solution. Compounded to 60mcg/ml of buprenorphine, with 1.9% alcohol base
- Doses of 15.9 mcg/kg/day trended towards buprenorphine having better outcomes
- Small study, only 24 patients
Paregoric

- Use has declined, though was historically used
- 0.4mg morphine equivalent per 1ml
- Ingredients include camphor (CNS stimulant), alcohol (45%), and benzoic acid (linked to CNS depression, seizures, and death in premature infants)
Clonidine

- Alpha-2 agonist, reduces noradrenergic activity by stimulation of inhibitory neurons
- Initially studied in 1970s/80s in opiate-exposed infants
- Half life 44-72 hours, may cause rebound tachycardia and hypertension
- Often used 2nd line behind opiates. Studies comparing clonidine with either morphine, DTO, or methadone, all show a decrease in treatment duration and opiate dosing
- Dose typically 0.5-1.25 mcg/kg q4-6 hours, compounded into a 0.1mg/ml solution
- Target serum concentration of 0.8-1 ng/ml provides adequate sedation, however not routinely measured
Phenobarbital

- Treatment of choice for sedative-hypnotics, and non-opiate NAS
- Used as an adjunct to methadone or morphine
- Enhances GABA activity
- Mainly causes CNS depression; decreased irritability and hyperactivity
  - No effect on purely opioid receptor activity, such as improving diarrhea
Downsides:
- Rapid tolerance
- Drug interactions
- 15% alcohol
- Oversedation
- One study showed that the average time to titrate OFF phenobarbital was 3.5 months

When compared to clonidine as an adjunct, phenobarbital had no significant impact on inpatient treatment time, but did prolong the outpatient/total treatment course
However, still worth it?

- Coyle et al, Pediatrics 2002.
- Compared DTO + placebo, to DTO + phenobarbital
- Average length of stay was 79 days, compared to 38
- Cost of stay: $69,200, vs $33,344
Breast Feeding

- Considered safe for mothers taking methadone or buprenorphine, and if they have Hepatitis B or C
- Jansson et al (Pediatrics 2008) showed breast milk concentrations in methadone-using mothers ranged from 21-462 ng/ml
- The infant serum levels ranged 2.2 to 8.1ng/ml, and did NOT correlate to their breastfeeding
- Abdel-Latif et al (Pediatrics 2006)
  - Decreased LOS by 5 days
  - Of those in study, 53% of breast-fed infants required pharmacotherapy, vs 79% of formula-fed infants
NB:

- These findings do NOT translate over to hydrocodone and oxycodone, which ARE present in high concentrations in breast milk.
- May cause infant sedation
Discharge Criteria

- Infant without major withdrawal signs, sleeping, and gaining weight
- Stable, or down-trending NAS scores and medication requirements
- Able to discharge to a stable home environment
Due to high concomitant rates of abuse and neglect from parents that abuse drugs, physicians should consider multi-disciplinary approach

- Child Protective Services
- Mental health services
- Early intervention programs - high frequency health care visits may improve cognition and social development
- Possible Individual Education Plans when older
Long-term Sequelae

- It’s difficult to attribute long term complication to drug use only
  - For example, women that abuse illegal drugs often use multiple drugs and have mental health disorders
  - Effect of violence in the parents’ lives?
  - Socioeconomic status (access to nutrition, health care, etc)
- One theory hypothesizes that the developing fetus develops physiologic “set points” based upon it’s uterine environment; these become maladaptive once born
  - Eg: maternal vagal tone in methadone-using mothers correlated with NAS severity scores
Still under investigation

- Pediatrics 2014: “No significant adverse long-term outcomes were reported among neonates who were exposed in utero to SSRIs, SNRIs, TCAs, benzodiazepines, or methamphetamines.”
- Yet, “… no longitudinal follow-up studies have extended beyond the first few years of life.”

- Research continues ...
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