Your New Patient is Being Treated for Neonatal Abstinence Syndrome

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Some slides and concepts are borrowed from Karen Buchi, MD with her permission
Disclosures

- In the past 12 months, I have not had a significant financial interest or other relationship with the manufacturer(s) of the product(s) or provider(s) of the service(s) that will be discussed in my presentation.

- This presentation will include discussion of unapproved or “off-label” uses of pharmaceuticals because few/no drugs have been labeled for the treatment of neonatal abstinence syndrome in newborns, specifically: clonidine, phenobarbital, morphine, diluted tincture of opium, or methadone
Your Patient Has Joined the Growing Crowd of Newborns with Neonatal Abstinence Syndrome
Objectives

The audience will:

• be able to discuss the advantages and disadvantages of the treatment options for the Neonatal Abstinence Syndrome with morphine, methadone, phenobarbital, and clonidine

• Incorporate the mechanisms of action of treatments for NAS into their weaning strategies
Scope of the Problem

- Nationally, illicit drug use occurs in 16.2% of pregnant teens & 7.4% of pregnant women aged 18 to 25 years.
- From 2000 to 2009, the discharge diagnosis of NAS has increased 282% with an increased cost from $190 Million to $720 Million.


Patrick et al. JAMA. 2012;307(18):1934-1940
Costs of Inpatient Treatment of NAS is Driving Treatment to the Outpatient Clinic

- Morphine or methadone with phenobarbital remain the mainstays of treatment, but clonidine is increasing
  - Each of these drugs has specific pharmacologic features that affect how to use them in specific patients
• G4P3 single mother treated with oxycodone/acetaminophen (Percocet™) for 2 years after automobile accident
• Delivered 37 wk EGA, male, 2960 gm
• Works M-F to maintain insurance while baby sitter cares for other children & could not spend much time in the hospital with newborn
• Well known to your practice as a reliable caregiver who utilizes evening clinic
NAS after Birth

- Infant developed symptoms of NAS at 28 hrs after birth
  - Irritable, inconsolable, emesis, watery stools with modified Finnegan scores of 9-12
- Treated with morphine
  - 0.05 mg/kg q3 h with feeds, up to 0.15 mg/kg/dose by day 3 then weaned to 0.10 mg/kg/dose for 2 days
  - discharged to you to continue morphine wean at home because of difficulties of mother visiting and childcare
Morphine Metabolism Alters its Effects
Morphine is glucuronidated into 2 different metabolites with quite different properties.
Morphine Metabolism in Newborns

Morphine infusions to newborns show the differences in metabolite formation

$M_3G/M_6G=15$

Tapering Morphine During Parent Care

- Parents must be educated about signs of withdrawal
- Most hospitals still use a modified form of the Finnegan scoring system and the parents are likely aware of the features
- The Finnegan is a neonatal scoring tool; normal older infants develop behaviors that can increase the score
- Focus the parents on degrees of irritability, diarrhea and emesis that prevent sleep, feeding and adequate nutrition
Morphine Tapering for NAS

- Few studies compared different rates of tapering morphine
- As morphine is tapered, the Mu-opioid surface receptors and neurons’ intracellular chemical state must normalize
- Tolerance for tapering varies among infants
  - Traditional rate is 10% every 2-4 days to 0.015-0.02 mg/kg, but faster and slower may be needed
  - Educate family about signs of withdrawal
- See pt weekly for wt checks, new morphine Rx, warn mother against using her drugs to treat NAS
Clues to Morphine Dysphoria

- The preverbal infant won’t tell you that morphine makes them feel irritable and restless, but their behavior does
22 year old, G2P1001 married mother in a methadone maintenance program (95 mg/d) after quitting heroin

36 wk EGA, 3100 gm female at birth, now 35 days old

NAS developed on day 3 after birth with irritability, fever, watery stools unresponsive to comfort measures

- Control required morphine 0.2 mg/kg q6h, phenobarbital 20 mg/kg then 4 mg/kg qd, clonidine 1 mcg/kg/dose q6h
- Morphine changed to methadone at 25 days of age
- Current Rx: **methadone** 0.14 mg/kg q6h, **clonidine** 1 mcg/kg q6h and **phenobarbital** 2 mg/kg q12h
- Mom breast feeds, but her milk is decreasing
Difficult to Control NAS
Methadone, Phenobarbital, Clonidine

- Taper the opioid first to allow the neuron to return to a baseline state of intracellular chemistry (electrolytes, cAMP, various protein kinases), surface mu receptors
- Tolerance of methadone taper is hard to predict
  - Clearance in neonates >1 wk of age & infants = that of children and adults (Ward et al. Ped Anesth 2014;24:591)
  - Traditional 10% every week
The rate of weaning is not tolerated the same by all infants.

The half-life of morphine and its glucuronides is
Neonatal Discontinuation Syndromes vs Neonatal Abstinence Syndrome (NAS)

- Neonatal Discontinuation Syndromes: spectrum of neonatal behaviors observed in drug-exposed infants after in utero exposure to different chemicals as the chemical is cleared from the body
  - methamphetamine, cocaine, nicotine, caffeine, SSRI’s
- Neonatal Abstinence Syndrome—used to refer to signs and symptoms after birth following removal from transplacental opioids or benzodiazepines; effects are often prolonged
Exposures: Rarely a Single Substance

- Mixed exposures are the rule, not the exception
  - mothers in methadone maintenance: 75% smoke tobacco, 40% drink ethanol ([*Pediatrics* 2006;118;1149])
- Expect behavioral effects of caffeine, nicotine and alcohol to be combined with those of narcotics, cocaine and methamphetamine
- The time course of these signs and symptoms helps distinguish which is the major contributor to poor adaptation at birth
“Next Generation” Studies
Careful Measure of Environment, Parenting

- **Maternal Lifestyle Study**
  - Longitudinal cohort study focusing on cocaine exposure
  - Mother-infant dyads enrolled at delivery, 1993-1995
  - Outcome studies published starting in 2001

- **Infant Development, Environment, and Lifestyle Study (IDEAL)**
  - Longitudinal cohort study of methamphetamine exposure
  - Mother-infant dyads enrolled at delivery, 2002-2003
  - Outcome studies published starting in 2006
  - Primary Outcome Measures: Birth Weight, Gestational Age, Congenital Anomalies, CNS involvement
Marijuana

- Low Birth Weight
  - Small and inconsistent effects on birth weight
  - MLS: No association found

- Prematurity
  - MLS and IDEAL: No association found

- CNS Involvement
  - Neonatal period: no significant effect
Nicotine

- Leading cause of low birth weight in US
- Dose-related impact on the risk of prematurity
- CNS Involvement
  - Newborn: Neurobehavioral differences
    - Newborn period (24-48 hours): Dose related changes
    - More aroused, reactive, hypertonic and required more handling
    - 10 to 27 days: worse self-regulation, normal tone
  - SIDS: Established association

Cocaine

- Low Birth Weight
  - More consistently observed than for other illicit drugs
  - MLS: 536 grams difference

- Lower gestational Age
  - MLS: 8.4 day difference

- CNS Involvement – No “abstinence syndrome”
  - Newborn: subtle neurobehavioral effects, no withdrawal syndrome
  - Longer term: effects are inconsistent and subtle, but still significant
Methamphetamine

- **Low Birth Weight**
  - IDEAL Study: 200 gram difference, SGA: 19% vs 8.5%

- **Gestational Age**
  - IDEAL Study: -1.4 week difference

- **CNS Involvement – No “abstinence syndrome”**
  - **Newborn**
    - Lower arousal and more stress signs, no withdrawal syndrome
  - **Long term**
    - No differences in mental development at ages 1, 2, and 3
Antidepressant Use in the U.S.

- 1996-2005: Antidepressant treatment doubled 5.84% to 10.12% = 13.3 to 27.0 million persons
  - Olfson et al: Arch Gen Psych. 2009;66:848
- 2007 CDC: Antidepressants most prescribed drugs in U.S.
- New major/minor depression in pregnancy - 14.5%
  - Wisner. Depression Anxiety 2010;27:695
- 1998-2005: Antidepressant use in pregnancy increased 324% (2.5% to 8.1%)
  - National Birth Defects Prevention Study
Neonatal Outcomes After Late Pregnancy Antidepressant Exposure

- Up to 31% of neonates exposed to SSRI's, SNRI's late in pregnancy exhibit neurobehavioral signs; resolve within 4 days to 2 weeks
  
  *NEJM* 1996;335:1010; *JAMA* 2005;293:2372; *Pharmacopsychiatry* 2009;42:95;

- Preterm Birth (OR 1.96)
- Low Apgar Scores (OR 2.33)
- Respiratory Distress (transient usually) (OR 2.21)
- Neonatal Convulsions (OR 1.90)
- Hypoglycemia (OR 1.62)-TCA's
  
  *Arch Pediatr Adolesc Med* 2004;158:312
### Many Selective Serotonin Reuptake Inhibitors & Serotonin/Norepinephrine Reuptake Inhibitors

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<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
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<th>Trade Name</th>
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<tbody>
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<td>Citalopram</td>
<td>Celexa, Cipramil, Dalsan, Emocal, Recital, Sepram, Seropram</td>
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<td>Effexor</td>
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<td>Escitalopram</td>
<td>Cipralex, Esertia, Lexapro</td>
<td>Desvenlafaxine</td>
<td>Pristiq</td>
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<td>Fluoxetine</td>
<td>Dumyrox, Favoxil, Fevarin, Luvox and Mvox</td>
<td>Duloxetine</td>
<td>Cymbalta</td>
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<tr>
<td>Fluvoxamine</td>
<td>Dumyrox, Favoxil, Fevarin, Luvox and Mvox</td>
<td>Tramadol</td>
<td>Tramal, Ultram</td>
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<tr>
<td>Paroxetine</td>
<td>Aropax, Deroxat, Paroxat, Paxil, Rexetin, Sereupin, Seroxat, and Xetanor.</td>
<td>Sibutramine</td>
<td>Meridia, Reductil</td>
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<tr>
<td>Sertaline</td>
<td>Lustral, Serlain and Zoloft</td>
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# Neonatal SSRI/SNRI Discontinuation Syndrome in 57 Neonates (JAMA 2005;293:2372)

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<th>Sign</th>
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<th>Sign</th>
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<td>Irritability</td>
<td>35</td>
<td>Screaming</td>
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<tr>
<td>Hypertonia</td>
<td>30</td>
<td>Vomiting</td>
<td>7</td>
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<tr>
<td>Jitteriness</td>
<td>24</td>
<td>Hypotonia</td>
<td>7</td>
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<tr>
<td>Trouble Feeding</td>
<td>23</td>
<td>High Pitched Cry</td>
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<tr>
<td>Tremor</td>
<td>23</td>
<td>Hypothermia</td>
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<tr>
<td>Agitation</td>
<td>14</td>
<td>Shivering</td>
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<tr>
<td>Seizures</td>
<td>14</td>
<td>Respiratory Distress</td>
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<tr>
<td>Tachypnea</td>
<td>12</td>
<td>Hyper-reflexia</td>
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<tr>
<td>Posturing</td>
<td>10</td>
<td>Jerkiness</td>
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<tr>
<td>Excessive crying</td>
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<td>EEG Abnormalities</td>
<td>4</td>
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<tr>
<td>Trouble Breathing</td>
<td>9</td>
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</table>
Long Term Outcomes After Perinatal SSRI/SNRI Exposure

- Most studies & reviews show no long term differences from control infants after the neonatal period
  - Am J Psychiatry: 2002;159:2055-61
  - Pharmacotherapy: 2007;27:546-52
  - Clin Ther: 2009;31 Pt 1:1426-53

- Untreated maternal depression during and after pregnancy is hazardous to maternal, fetal and infant health

- Support appropriate maternal treatment
Fetal Alcohol Syndrome

- Fetal alcohol syndrome (FAS) occurs in newborns & children following extensive perinatal exposure by alcoholic mothers who drank daily or intermittently heavily in binges throughout pregnancy
  - Lemoine et al. Quest Med 1968;25:476
  - Clarren et al. NEJM 1978;298:1063
- Prenatal growth deficiency
- Specific pattern of minor abnormalities
- CNS abnormalities (microcephaly, developmental delay, ADD, etc.)
Fetal Alcohol Syndrome Terminology

- Fetal Alcohol Syndrome occurs with alcoholism or binge drinking throughout pregnancy
- Some authors feel no fetal ethanol exposure is safe
  Clarren http://www.indiana.edu/~engs/cbooik/tabcont.html
- Lesser changes attributed to ethanol, but not FAS
  - Fetal Alcohol Effect
  - Alcohol-Related Birth Defects
  - Partial FAS
  - Alcohol-Related Spectrum Disorder
  - Alcohol-Related Neurodevelopmental Disorder
Facial Features of FAS

Discriminating Features
- Short palpebral fissures
- Flat midface
- Indistinct philtrum
- Thin upper lip

Associated Features
- Epicanthal folds
- Lownasal bridge
- Minor ear anomalies
- Short nose
- Micrognathia

Streissguth and Little (1994).
Fetal Alcohol Syndrome (FAS)
CNS Dysfunction

- **Intellect:** Mild-moderate mental retardation*
- **Neurologic:** Microcephaly*
  - Hypotonia ‡
- **Behavioral:** Irritability in infancy*
  - Hyperactivity in childhood ‡

*Features Observed in >80% of Patients
‡Features Observed in >50% of Patients

Clarren & Smith. NEJM 1978;298:1068
FAS CNS Malformations Cerebellar Hypoplasia, Neuroglial Heterotopia

Clarren et al: J Pediatr 1978;92:64
FAS Can Improve in Function & Appearance
10 Year Follow-Up 72 Children

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Exam</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Developmental delay</td>
<td>90%</td>
<td>68%</td>
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<tr>
<td>Microcephaly</td>
<td>87%</td>
<td>65%</td>
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<tr>
<td>Thin upper lip</td>
<td>82%</td>
<td>72%</td>
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<tr>
<td>Postnatal growth deficiency</td>
<td>77%</td>
<td>43%</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>75%</td>
<td>23%</td>
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<tr>
<td>Hyperactivity</td>
<td>71%</td>
<td>52%</td>
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<tr>
<td>Abnormal palmar creases</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>Short Upturned nose</td>
<td>58%</td>
<td>38%</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>44%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Spohr et al: Lancet 1993;341:907
Poppy to Morphine in 1805

The Opium Poppy: *Papaver Somniferum*

Into the arms of Morpheus...

Morphine was isolated by 


*Papaver Somniferum* L.

The compound after Morpheus, the Greek god of dreams.
Narcotic Withdrawal in Newborns
A Problem As Old As Opium & Morphine

**Neonatal Abstinence Syndrome (NAS)**

- **1875:** report of “congenital morphinism”
- **1950-60’s:** “increasing trend in narcotic addiction”
- **1972:** methadone-exposed newborns, early report
- **2011:** perinatal prescription-narcotic dependence
  - Kellogg: *Am J Ob Gyn* 2011: 204: 259:e.1
TERMINOLOGY:
Opiate, Opioid, Narcotic, Endorphins

- **Opiate** - derived from poppies
  Morphine, DTO, laudanum, heroin = diacetylmorphine

- **Opioids** – includes opiates & synthetic derivatives
  - Fentanyl, methadone, oxycodone, hydrocodone

- **Narcotic** - opioid that produces somnolence
  (cocaine is often designated a narcotic within laws)

- **Endorphins** - endogenous opioid peptides
  - Enkephalins, dynorphins, beta-endorphins
TERMINOLOGY:
Tolerance, Dependence, Addiction

- **Tolerance** - condition in which more drug is needed to produce the same degree of pain relief
- **Dependence** - condition in which narcotics must be weaned to prevent withdrawal or abstinence
- **Addiction** - behavior pattern of drug use involving much effort and time spent using drugs, securing its supply with frequent relapse after withdrawal


NEWBORNS CANNOT BE ADDICTS
NAS Signs are Easily Recognized, But Pharmacology of NAS is Complex

- Neonatal Abstinence Syndrome (NAS) presents with a well recognized set of signs/symptoms:
  - Tremors, jitteriness, irritability, seizures
  - Tachycardia, tachypnea, sneezing
  - Diarrhea, emesis, sweating
  - Inability to feed adequately for nourishment

- Treatment is challenging & complex
  - Mechanisms of opioid analgesia, tolerance and abstinence are complex & not completely understood
  - Few, controlled randomized therapeutic trials
Onset of NAS

- NAS occurs in 55-94% of opioid exposed newborns
- Heroin: usually by 24 hr, seldom beyond 48 hr
- Methadone alone: 1-3 d, plus other drugs 0-5 d
  - *Addiction, 2003;98:785*
- Have not been able to obtain more details from early report of withdrawal as late as 2 weeks
Increasing Perinatal Narcotic Exposure

- 2010 National Survey of Drug Use and Health: 4.4 percent of pregnant women aged 15 to 44, were currently using illicit drugs
- NAS increased from 1.20 to 3.39 per 1000 births (Health Care Utilization Project) in last decade
  - *JAMA*. May 9 2012;307(18):1934-1940
Increasing Prescription Narcotic Use During Pregnancy at Mayo Clinic

Kellogg: Am J Ob Gyn 2011:204:259:e.1
Costs of NAS

- NAS costs in 125 newborns ≥ 34 wk, no anomalies compared to 3 matched controls
  - NAS increased per patient costs at birth by 435% vs matched controls, due mostly to increased length of stay
    - Intermountain Healthcare, Utah & Idaho; unpublished

- $720 Million = charges for NAS in 2009 in the U.S.
Opioids are Classified by Their Binding to Opioid Receptors ($\mu$, $\delta$, $\kappa$, ORL)

- **Mu, $\mu$:** classical analgesic receptor discovered in 1973
- **Delta, $\delta$:** analgesia, reduced dopamine release
- **Kappa, $\kappa$:** dysphoria, psychotic-like effects, analgesia, anti-analgesia especially against $\mu$ receptor effects
- **Receptor subtypes identified by ligand binding studies**
  - Distribution from brain to spine influences their effects
- **ORL (Opioid Receptor-Like Protein) later called the N/OFQ (Nociceptin or Orphanin FQ) receptor-hyperalgesia, analgesia**

Drugs Associated with Neonatal Abstinence Syndrome

Opioids
- Heroin
- Methadone
- Fentanyl
- Morphine
- Meperidine
- Buprenorphine

Less Potent Opioids
- Propoxyphene HCl (Darvon, Darvocet)
- Codeine
- Pentazocine (Talwin)

CNS Depressants
- Tranquilizers and sedatives
- Chlordiazepoxide (Librium)
- Lorazepam (Ativan), diazepam (Valium) other benzodiazepines
- Alcohol
Onset of NAS

- **Factors to consider**
  - Timing and dose of all drug(s) used before delivery
  - Maturity, nutritional status, and intrinsic health of the neonate
- **Majority start showing signs within 72 hours**
  - Range is from minutes to hours after birth to up to 2 weeks (?)
  - Late onset of withdrawal symptoms is not described in detail. May relate to stopping breast feeding, but Dr. Kandall pointed out that breast feeding was rare in the 1970’s
Neonatal Abstinence Syndrome

Behavioral Scoring Systems

- Neonatal Abstinence Scoring System
  - Finnegan, (Addictive Diseases: an Internat J. 1975;2:141
  - Modified (slightly shortened) Finnegan Scoring Systems are widely used

- Neonatal Drug Withdrawal Scoring System
<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Score</th>
<th>AM</th>
<th>PM</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Excessive High Pitched Cry</td>
<td>2</td>
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<tr>
<td>Continuous High Pitched Cry</td>
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<tr>
<td>Sleeps &lt; 1 Hour After Feeding</td>
<td>3</td>
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<tr>
<td>Sleeps &lt; 2 Hours After Feeding</td>
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<td>Sleeps &lt; 3 Hours After Feeding</td>
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<td>Hyperactive Moro Reflex</td>
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<td>Markedly Hyperactive Moro Reflex</td>
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<tr>
<td>Mild Tremors Disturbed</td>
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<td>Moderate-Severe Tremors Disturbed</td>
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<td>Mild Tremors Undisturbed</td>
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<td>Moderate-Severe Tremors Undisturbed</td>
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<tr>
<td>Increased Muscle Tone</td>
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<td>Myoelonic Jerks</td>
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<td>Generalized Convulsions</td>
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<td>Fever &lt; 38.3</td>
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<td>Respiratory Rate &gt; 60 with retractions</td>
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<td>Excessive Sucking</td>
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<td>TOTAL SCORE</td>
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<td>INITIALS OF SCORER</td>
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<tr>
<td>Signs</td>
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<td>--------------------------------------------</td>
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<tr>
<td>Tremors (muscle activity of limbs)</td>
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<td>Minimally increased when hungry or disturbed</td>
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<td></td>
<td>Moderate or marked increased when undisturbed -- subside when fed or held snugly</td>
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<td></td>
<td>Marked increase or continuous even when undisturbed, going on to seizure-like movements</td>
<td></td>
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<tr>
<td>Irritability (excessive crying)</td>
<td>None</td>
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<tr>
<td></td>
<td>Slightly increased when disturbed or hungry</td>
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<tr>
<td></td>
<td>Moderate to severe when undisturbed or hungry</td>
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<tr>
<td></td>
<td>Marked even when undisturbed</td>
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<tr>
<td>Reflexes</td>
<td>Normal</td>
<td></td>
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<tr>
<td></td>
<td>Increased</td>
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<tr>
<td></td>
<td>Markedly increased</td>
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<tr>
<td>Stools</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Explosive, but normal frequency</td>
<td></td>
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<tr>
<td></td>
<td>Explosive, more than 8 per day</td>
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<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td></td>
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<tr>
<td></td>
<td>Increased</td>
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<tr>
<td></td>
<td>Rigidity</td>
<td></td>
<td></td>
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<tr>
<td>Skin abrasions</td>
<td>No</td>
<td></td>
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<tr>
<td></td>
<td>Redness of knees and elbows</td>
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<tr>
<td></td>
<td>Skin breakdown</td>
<td></td>
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<tr>
<td>Respiratory rate/min</td>
<td>&lt; 55</td>
<td></td>
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<td></td>
<td>55-75</td>
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<tr>
<td></td>
<td>&gt;76</td>
<td></td>
<td></td>
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<tr>
<td>Repetitive sneezing</td>
<td>No</td>
<td></td>
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<td></td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>Repetitive yawning</td>
<td>No</td>
<td></td>
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<td></td>
<td>Yes</td>
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<tr>
<td>Vomiting</td>
<td>No</td>
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<td></td>
<td>Yes</td>
<td></td>
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<tr>
<td>Fever</td>
<td>No</td>
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<td>Yes</td>
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</table>
Non-Pharmacologic Treatment-1st

• Goal
  • Relieve symptoms that are interfering with
    • Physiologic stability
    • Weight gain
    • Ability to be consoled
    • Sleep
  • Improve mother-infant interactions
Non-Pharmacologic Treatment-1st

- **Nursing Support**
  - swaddling with soft blankets
  - quiet, dark environment
  - frequent small feedings of hypercaloric formula
  - try a pacifier with simple syrup (?endorphins)
  - skin care
  - watch for other disease processes
  - organize care to minimize handling
  - swings – helpful for some
  - determine level of stimulation infant can tolerate

Non-Pharmacologic Treatment-1st

- **Parent teaching**
  - Explain how withdrawal is affecting the infant’s ability to cope with stimulation
  - Explain how to decrease stimulation
  - Help parents find out how much the infant will tolerate
NAS: Pharmacologic Treatment

Morphine

- Morphine solution (0.4 mg/ml of morphine)
  - Start at 0.05 mg/kg with feedings every 3-4 hours
  - Increase by 0.05 mg/kg q 3-4 hrs as needed to control symptoms
  - **Goal is to control irritability and poor feeding well enough to be cared for at home**
  - Keep at stable dose for 3-5 days, then wean by 10% per day (tradition vs prospectively studied)
- Morphine treatment longer than 2 weeks may lead to dysphoria & restlessness from morphine-3 glucuronide
Phenobarbital

- does not control gastrointestinal symptoms
- sometimes better for behavioral symptoms
- loading dose of 16-20 mg/kg per 24 hours
- maintenance dose of 2 to 8 mg/kg per 24 hours, increase dose with age as clearance increases
- Combined with morphine shortened hospital stay in a study at the Univ of Utah (unpublished)
NAS: Pharmacologic Treatment
Methadone: less sedating

- Methadone (1 mg ≈ 1 mg morphine or 1 µg fentanyl)
  - 0.05-0.1 mg/kg q 6 hours
  - Increase by 0.05 mg/kg until symptoms are controlled, then can give q 12-24 hours
  - During start of methadone, treat acute NAS symptoms with a shorter acting opioid - morphine
  - Wean by 0.05 mg/kg or 10% per week, per month???
- Kinetics in newborns are just being reported
- Racemic mixture: R-methadone is analgesic; S-methadone affects cardiac conduction in adults
NAS: Pharmacologic Treatment
Methadone

- Some pediatricians stabilize newborns with methadone and discharge them with close follow-up
- Wait 1-2 months to start reducing the dose
- Reduce the dose over the next 6 months
- Requires a reliable parent/physician relationship
Buprenorphine-Complicated Pharmacology

Buprenorphine-partial agonist/antagonist
- Mu -partial agonist, ORL₁-partial/full agonist, Kappa-antagonist
- **Binds mu so tightly it can displace agonist morphine or methadone and cause acute withdrawal**
- Buprenorphine overdose: only partially reversed by naloxone

Norbuprenorphine-active metabolite
- Agonist - δ, ORL-1 receptors
- Partial agonist-κ, μ receptors
- Antagonized by buprenorphine
Buprenorphine Products
(All Off-label in Newborns)

- Buprenorphine, no active additives
  - Buprenex™, Subutex™
- Buprenorphine + Naloxone, 4:1
  - Suboxone™, supposed to reduce i.v. use, but the dose of naloxone is too low
  - Naloxone is not well absorbed sublingually
- Buprenorphine during pregnancy
  - Still causes NAS, but shorter & milder, may relate to lower opioid equivalent dose
    - Drug and Alcohol Dependence 2008;96:69–78
NAS: Pharmacologic Treatment

Clonidine

- Alpha₂ Adrenergic Agonist, antihypertensive: presynaptic inhibitor norepinephrine/dopamine release
- Reduces signs/symptoms NAS while neuron reverses its tolerance to opioids
- Morphine + clonidine 1 µg/kg/dose q 4-6 hr shortens opioid treatment for NAS (*Pediatrics* 2009;123;e849-e856)
- Clearance increases rapidly to 70% adult rate by 1 mo
- Single drug treatment for NAS-limited experience
- Hypertension can occur as it is tapered
NAS: Pharmacologic Treatment
Drugs NOT to Use

- Diazepam
  - not effective, reduces feeding
- Paregoric
  - too many additives
- Diluted Tincture of Opium
  - too many additives
  - (Regardless of the Committee on Drugs Statement Pediatrics 1998;101;1079-1088)
- See more recent statement: Pediatrics 2012;129;e540;
Neonatal Abstinence Syndrome

- Length of treatment/Duration of hospitalization HIGHLY variable
  - Should be observed for several days, especially with methadone exposure
  - Stop focusing on the “number” after the initial week
  - Focus on length of sleeping, ability to gain weight, ability to be cared for by a “reasonable lay person”
  - Evaluate safety of the home environment
- Consider the developmental age of the infant
Intrauterine Drug Exposure: What’s a Pediatrician to Do?

- Discharge issues
  - Caretaker - evaluate with social work
    - Safety of home environment
    - Support systems
  - Child protection involvement
- Home on meds?
  - Outpatient follow-up dependent on pediatric care provider’s comfort and familiarity with NAS treatment
    - Phenobarbital
    - Methadone
    - Clonidine
Breastfeeding

- Check prenatal labs for infectious disease risk
- Check drug screens for poly-drug use
- Safe to breastfeed with methadone
  - Probably does not prevent NAS, but some studies have found it may help;
  - **NAS may begin if breast feeding stops abruptly**
  - Concentrations in breast milk are low and not related to maternal dose *Pediatrics* 2008:
  - McCarthy and Posey estimate 0.05 mg of methadone/day through the breast milk *J Hum Lact* 2000;16(2):115-120
Intrauterine Drug Exposure: What’s a Pediatrician to Do?

- Be aware of potential neonatal problems based on a careful history and testing for potential perinatal exposures
- Recognize substances with temporary discontinuation syndromes
- Manage Neonatal Abstinence Syndrome, first non-pharmacologically, then with medications if needed
- Insure that the home environment is safe
- Close follow-up for medical/developmental problems
- Arrange early intervention when indicated
- Involve Child Protection Agency when needed