NEUROBIOLOGY OF NEONATAL ABSTINENCE SYNDROME: A GUIDE TO THERAPY

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Johns Hopkins School of Medicine

Learning objectives:
To understand the neurobiology mediating the different types of withdrawal from illicit drugs: physical and psychological

To understand why clonidine may be an effective adjunct treatment choice for individuals with moderate to severe withdrawal from opiates

Past Month Illicit Drug Use among Persons Aged 12 or Older: 2012

INCIDENCE OF NAS ACROSS THE COUNTRY

Tennessee: 10-fold increase (12yrs)
0.7 per 1,000 live births in 1999,
8.5 per 1,000 live births in 2011.

Kentucky: 11-fold increase (10yrs)
1.2 cases per 1,000 live births in 2001
13.2 cases per 1,000 live births in 2011

Florida: 3-fold increase (6 yrs)
2.31 per 1,000 live births in 2007
7.52 per 1,000 live births in 2011.

Vermont: 8-fold increase (8 yrs)
3 per 1,000 deliveries in 2002
26 per 1,000 deliveries in 2010

Washington: 3-fold increase (6 yrs)
1.2 per 1,000 live births in 2000
3.3 per 1,000 live births in 2008.

What drug exposures cause or contribute to withdrawal or poor neonatal adaptation
- Opiates: methadone, buprenorphine, heroin,
- Prescription drugs:
  - Vicodin, OxyContin, Percocet
- Benzodiazepines
- Stimulants: cocaine, methamphetamine
- Cannabinoids
- Tobacco
- SSRIs
Shift from abuse of classical opioids such as heroin, morphine and methadone to abuse of prescription opioids such as hydrocodone, hydromorphone and oxycodone.

Prescription of opioids in the U.S. during the last ten years

<table>
<thead>
<tr>
<th>Year</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>174 million</td>
</tr>
<tr>
<td>2011</td>
<td>238 million</td>
</tr>
</tbody>
</table>

Prescription drug abuse:
- Women 15-17 years of age:
  - 23% of pregnant women
  - 13% in non-pregnant women

OPIOIDS:
- Vicodin
- OxyContin
- Codeine
- Fentanyl

- Diminish perception of pain
- Addiction
- Dependence
- Constipation
- Slow respiration
- Death

DEPRESSANTS:
- Valium
- Xanax
- Ambien

- Calming
- Drowsiness
- Addiction
- Dependence
- Uncoordinated
- Slow respiration
- Decrease heart rate
- Death

STIMULANTS:
- Adderall
- Ritalin

- Alertness
- Addiction
- Dependence
- Irregular heartbeat
- High blood pressure
- Heart failure
- Seizures
- Paranoia
- Death

OPIDATES: 
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ONE in FIVE Idaho students report taking a prescription drug without a physician's prescription at least once during their lifetime (Idaho Youth Risk Behavior Survey, 2011)

In 2010, an Idaho citizen died every 45 HOURS because of a drug-induced death caused by drug, prescription, or over-the-counter drug use. 250% increase since 2000. (Idaho Vital Statistics, 2010) This rise is greatly attributed to the increase in prescription drug abuse.

From 2005 to 2010, Idaho addiction treatment facilities experienced a SEVEN FOLD increase in percent of opioid admissions as the primary substance of abuse. (SAMHSA, Idaho Treatment Episode Data Set)

In 2011, more Americans (8.1 MILLION) reported the nonmedical use of prescription drugs within the preceding month than had used cocaine, heroin, hallucinogens, and inhalants combined. (SAMHSA NSDUH 2011)

54% of prescription opioids being used for nonmedical purposes are obtained from a friend or relative for free, with these friends or relatives most often obtaining them from 1 physician (82%) (SAMHSA NSDUH 2011)

EVERY HOUR, one baby in the US is born suffering from opiate withdrawal. (National Institute of Drug Abuse, 2012)
Tobacco exposure ---toxicity vs withdrawal---

Only tobacco-exposed infants – within 24 hrs of birth:
- excitable hypertonic, required more handling and
- More stress/abstinence signs
- specifically in the central nervous system (CNS), GI, and visual areas.
- Resolved with in 24-48 hrs

Law et al, Lester: PEDIATRICS Vol. 111 No. 6 June 2003

Predictors of severity of NAS

Increase Severity
- Polymorphisms in µ-opioid receptor OPRM1, variant A11AG and catechol-o-methyltransferase (COMT)
- Higher maternal dose methadone during last trimester
- GA >36 wks
- Lower maternal weight at delivery
- High infant BW
- Benzodiazepines
- SSRI exposure
- Cigarettes smoke 24 hrs prior to delivery

Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002–2012

A few important definitions

- **Tolerance**-
  - Loss of effect following repeated treatments such that a higher dose is required for equivalent effect

- **Dependence**—Superactivation of cAMP
  - **Physical signs**: withdrawal (autonomic and somatic signs associated with drug absence)
  - **Psychological**—(addiction) –
    - loss of control over drug use (impulsivity and compulsivity) –

In utero exposure

<table>
<thead>
<tr>
<th>Opiate Exposure</th>
<th>Heroin, Methadone oxycodone buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>24-72 hours After birth 4-5 days for buprenorphine</td>
</tr>
<tr>
<td>Incidence</td>
<td>Heroin &gt;90% Methadone – 50-90% Oxycodone – 5-6% Buprenorphine- 20-70%</td>
</tr>
</tbody>
</table>
**Clinical Signs**

- **W**akefulness
  - Ibbillability
- **T**remors, **T**emperature **I**nstability, **T**achypnea
- **H**yperactivity, High Pitch **C**ry, Hypertonia, **H**yper-reflexia
- **D**iarrhea, Dysfunctional **S**uck and **S**wallow
- **R**ub **M**arks, Respiratory **D**istress, **R**hinorrea, **R**eflux
- **A**pnea, **A**lkalosis (respiratory), **A**cidosis (metabolic)
- **W**eight **L**oss
- **A**utonomic **D**ysfunction (sneeze, yawn, sweating)
- **L**acrimation

**Norepinephrine neurocircuity in the brain mediates the physical signs of withdrawal leading to Elevated Sympathetic Output**

**HPA axis – CRF – ACTH – ADRENALS-CORTISOL-EPI and NE**

**Upregulation of the cAMP pathway in opiate dependence in other regions**

- **Myenteric plexus of gut** – constipation
  - Tolerance to opiate-induced reduction in intestinal motility and increase in motility during withdrawal
- **Dorsal horn of Spinal Cord** – hyperalgesia
  - Tolerance to opiate-induced analgesia
- **Multiple Brain regions** – dysphoria,
  - involved in psychological addiction

**Neurocircuitry: Reward Pathway**

Dopamine

- Ventral Tegmental Area
- Prefrontal cortex
- Nucleus accumbens
- Chocolate/Exercise
- Wakefulness
- Irritability
- Tremors, Temperature Instability, Tachypnea
- Hyperactivity, High Pitch Cry, Hypertonia, Hyper-reflexia
- Diarrhea, Dysfunctional Suck and Swallow
- Rub Marks, Respiratory Distress, Rhinorrea, Reflux
- Apnea, Alkalosis (respiratory), Acidosis (metabolic)
- Weight Loss
- Autonomic Dysfunction (sneeze, yawn, sweating)
- Lacrimation

**Summation of cellular events**

- Acute responses to opiate exposure in a neuron in the LC

**LC neurons**

- cellular adaptation after chronic exposure

- $\alpha_1$ receptors,
- $\beta_1$ receptors
- Vasodilation, smooth muscle,
- Diaphoresis, Tachycardia,
- Hypertension, GI irritability

- Adenylyl cyclase
- CAMP
- PKA
- NE
- NE
- NE
- NE
- NE
- NE
- NE
- NE
NALTREXONE PRECIPITATED OPIATE WITHDRAWAL IN METHADONE ADDICTED HUMAN SUBJECTS: EVIDENCE FOR NORADRENERGIC HYPERACTIVITY

Dennis S. Charney; D. Eugene Redmond, Jr.; Matthew P. Galloway; Herbert D. Kleber; George R. Heninger; Michelle Murberg; Robert H. Roth

Life Sciences 1984 Vol 35 pp 1263-1272

Direct correlation between the abstinence scores and plasma MHPG levels (a biomarker for centrally released NE) in adult humans during opiate withdrawal

Opioids used to treat NAS in infants

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Morphine</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Action</td>
<td>Mu-receptor agonist</td>
<td>Mu-receptor NMDA antagonist</td>
<td>partial µ-opioid agonist, high affinity for and slow dissociation 'ceiling effect'</td>
</tr>
<tr>
<td>Ethanol content</td>
<td>0%</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Variable, &lt;40%</td>
<td>36–100%</td>
<td>NA</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>&lt;20 High lipid soluble</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Metabolic pathway (metabolites)</td>
<td>glucuronidation (morphine-6-glucuronide (active); norbuprenorphine-3-glucuronide (inactive))</td>
<td>Hepatic N-dealkylation (norbuprenorphine (active)) and glucuronidation of active metabolite</td>
<td></td>
</tr>
</tbody>
</table>

Methadone: CON

- Half life ~26 h in neonates compared with 8 h with morphine,
  - Drug accumulation – prolongs hospitalization
- Metabolism rates vary by factor of 100
- No single ratio for equianalgesic dosing can be found between morphine and methadone
  - Difficult to convert to morphine
Methadone: PRO

- Effective in treating opiate induced hyperalgesia, thus methadone may be useful in infants with iatrogenic NAS who also might have pain

-In 80% of cancer patients with uncontrolled pain or significant side effects, switching from morphine to methadone – better pain control and reduced side effects

J Clin Oncol. 2001;19:2898-2904

Buprenorphine for treatment of NAS in methadone exposed infants

On going RCT – Jefferson medical College, Thomas Jefferson

Given sublingual – dissolved in ETOH – Randomized – Not blinded

<table>
<thead>
<tr>
<th>Bupemorphine N=12</th>
<th>Morphine N=12</th>
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</thead>
<tbody>
<tr>
<td>13-39 mcg/kg/day (oral)</td>
<td>16-60mcg/kg/day</td>
</tr>
</tbody>
</table>

**Exclusion Criteria**

- Infants exposed to benzodiazepines

Infants who have severe NAS
May need 2nd agent to control symptoms

Phenobarbital as adjunct treatment for NAS based study with an N of 10 infants!!

Pediatric Neurologist avoid exposing neonates to phenobarbital longer than for treatment of the acute seizure episode

Because data from human and animal studies implicating cognitive delays and apoptosis, respectively

Review of the literature: Adverse effects of phenobarbital on outcome in humans:


For these reasons, at Johns Hopkins, we do not use Phenobarbital as adjunct therapy for treatment of NAS

But we do use CLONIDINE to directly target LC neuronal hyperactivity

Clonidine decrease sympathetic overactivity in response to withdrawal in adults

Representative recording of a patient addicted to opioids undergoing detoxification demonstrating the effects of opioid receptor blockade by naloxone during propofol anesthesia, and the effects of clonidine on arterial sympathetic activity in muscle and on arterial blood pressure.
Clonidine as an Adjunct Therapy to Opioids for Neonatal Abstinence Syndrome: A Randomized, Controlled Trial

Investigators:
Alex G. Agthe, M.D, George Kim, M.D., Kay Mathias, NNP, Raul Chavez-Valdez, M.D.
Tamorah Lewis, Lauren Jansson, M.D., Craig W. Hendrix, M.D., Ph.D., and Myron Yaster, M.D, Estelle B. Gauda, M.D

Funding: NIDA


Primary Endpoints:
- Length of treatment, defined as the need for any pharmacological treatment for NAS
- Amount of DTO (Diluted tincture of opium) needed to treat NAS

DTO: 0.4mg/ml of morphine

Inclusion Criteria:
- All newborns age 0 to 14 days who were prenatally exposed to opioids (methadone and/or heroin)
- NAS (moderate to severe) defined by two consecutive NAS-scores of ≥9 on the adapted Finnegan Scale,

INFANT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>CLONIDINE-DTO GROUP (N=40)</th>
<th>PLACEBO-DTO GROUP (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight – g</td>
<td>2863 ± 365</td>
<td>3045 ± 415</td>
</tr>
<tr>
<td>Gestational age – wk</td>
<td>38.5 ± 1.7</td>
<td>39.1 ± 2.0</td>
</tr>
<tr>
<td>Prenatal exposure – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>35 (87.5%)</td>
<td>35 (87.5%)</td>
</tr>
<tr>
<td>Morphine</td>
<td>26 (65)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>Cocaine with opioids</td>
<td>25 (62.5)</td>
<td>24 (60)</td>
</tr>
</tbody>
</table>

Summary of Study
- Clonidine combined with DTO (oral morphine) is effective in treating infants with NAS.

- Clonidine combined with DTO at dosage of 1mcg/kg every 4 hours was not associated with adverse cardiovascular outcomes in this newborn population.

- Infants with the worst signs of NAS benefited most from the addition of clonidine.

- More treatment failures were observed in the placebo+DTO group (5 vs 0) and seizures (3 vs 0).

- 3 Deaths in the overall cohort: Myocarditis, Homicide, SIDS—all after discharge to home.
  One infant developed SVT resolved

Infants in the clonidine group required less opiate after first 3 days of therapy

Mean DTO (mg/kg/day)

FACtORS THAT INCREASED LOS
Maternal BZD Use
And Bottle feeding

Concurrent drug exposures in women on Methadone Maintenance Therapy

<table>
<thead>
<tr>
<th>Tobacco</th>
<th>Alcohol</th>
<th>SSRIs</th>
<th>BZD</th>
<th>Marijuana</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>8.3</td>
<td>10.1</td>
<td>15.2</td>
<td>42.7</td>
<td>94</td>
</tr>
</tbody>
</table>

Pritham et al: JOGNN 41, 181-190 2012
**Benzodiazepines**

- Ativan (lorazepam)
- Valium (diazepam)
- Klonopin (clonazepam)
- Tranxene-SD (clorazepate)
- Xanax (alprazolam)
- Restoril (temazepam)
- Dalmane (flurazepam)

**Withdrawal associated with BZD exposure – later onset and protracted**

- Neonates exposed to benzodiazepines > LOT than those unexposed ~14 days
- Neonates exposed to BZD have a later presentation of NAS that is bimodal
    - Diazepam use by pregnant women can be associated with a later presentation of withdrawal symptoms in the neonate than that induced by the use of other drugs. Intensification of symptoms after 7-14 days of therapy
- BZD exposures on infant: -- floppy infant syndrome, or marked neonatal withdrawal symptoms -- mild sedation, hypotonia, and reluctance to suck, apneic spells, cyanosis, and impaired metabolic responses to cold stress, movement disorders

**Why**

- Highly lipophilic
- High intake in animal fat tissue
- Easy penetration into brain white matter
- Long retention in neural tissue
- High concentrations brain, the lungs, heart
- Fetal-maternal ratio of 1.2 to 2
- T1/2 in the neonate about 31 hours
- Tissues act as depot for BZD (diazepam-worst)

**Acute effects of THC exposure adults**

- problems with memory and learning
  - neurons in the information processing system of the hippocampus and the activity of the nerve fibers are suppressed by THC
- distorted perception
- difficulty in thinking and problem-solving
- loss of coordination
- increased heart rate
- anxiety
- panic attacks

**Marijuana smoke contains higher levels of certain toxins than tobacco smoke**

Daily or Almost Daily Marijuana Use in the Past Year and Past Month among Persons Aged 12 or Older: 2002-2012
Withdrawal from THC in adults

- Anxiety, irritability, physical tension, depression, and loss of appetite.
- Long T1/2 30 hrs
- Worse during the first 10 days of abstinence

Cannabis use during pregnancy psychosocial effects on children

- Prospective longitudinal assessments can increase the risk for ill behaviors (Goldschmidt et al., 2004; Day et al., 2011)
  - Cognitive deficit (Huizink & Mulder, 2006)
  - Drug seeking (Day et al., 2006)
  - Attention deficit (Leech et al., 1999)
  - Anxiety and depression (Leech et al., 2006)
  - Growth retardation (El Marroun et al., 2009)


Psychological dependence vs Physical Dependence

While essentially all drugs of abuse share similar signs and symptoms of psychological dependence (NAc-Dopamine) this is not the case for physical dependence (LC-NE)

Predictors of severity of NAS

- Increase Severity
  - Polymorphisms in µ-opioid receptor (OPRM1 variant A11AG) and catechol-methyltransferase (COMT)
  - Higher maternal dose methadone during last trimester
  - GA >36 wks
  - Lower maternal weight at delivery
  - High infant BW
  - Benzodiazepines
  - SSRI exposure
  - Cigarettes smoke 24 hrs prior to delivery

- Decrease Severity
  - Breastfeeding/Rooming In
  - Quiet environments
  - Buprenorphine
  - COCAINE

Reviewed in CLINICAL OBSTETRICS AND GYNECOLOGY ; 56,, 186–192 Addiction. 2012 Nov;107

What I hope you learned today

NAS from opiates is mediated by over activation of the sympathetic nervous system with a large contribution from excessive release of NE from LC neurons.

LC neurons contain opioid receptors and alpha 2 adrenergic receptors both of which cause reduction in NE output from LC neurons, making both receptors therapeutic targets for the treatment of NAS

11/3/2014
Alpha 2 adrenergic receptors have a restricted distribution in the brain. Clonidine binds to these receptors—reducing the release of NE.

GABA receptors are widely distributed throughout the brain. BZD and phenobarbital bind to these receptors throughout the brain.

What I hope you learned today

What I hope you will consider

Using this information to help guide targeted pharmacological therapies for the treatment NAS -

Advocate for properly conducted clinical trials in vulnerable populations to provide evidence –

When evidence is lacking -- use biology and physiology as a guide.

Pharmacological treatment of NAS:

1) Opiate replacement alone (morphine) followed by clonidine when adjunct therapy is required.
   - Clonidine is added when infant is requiring ≥ 0.2 mg (flat dose) of morphine every 4 hours (0.06 mg/kg q 4)
   - Clonidine dose 6–12mcg/kg/day divided q 3–6 hrs (may take 1–2 days to see full effect of clonidine)

2) Phenobarbital as adjunct therapy for the treatment of NAS should be avoided unless symptoms cannot be controlled with opiate/clonidine because of concurrent benzodiazepine withdrawal.

3) When phenobarbital is used for treatment of benzodiazepine withdrawal in neonates, it should be used at the lowest effective dose for the shortest period of time.

Thank you for your Attention

What I hope you remember

- Phenobarbital similar to BZD, enhance the binding of GABA to the GABA A receptor
- Depresses neuronal activity throughout the entire brain accounting during period of development
- Overall neuronal depression throughout the brain may be contributing to adverse effects on the developing nervous system

What I hope you will consider

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Thank you for your Attention
Positive urine toxicology screens in mothers and infants
n= 114
4 wks prior to delivery

Drug use last 30 days: BZD 38%; cocaine 3.4%; marijuana 35%

Prospective cohort study: 114 mother/infant dyads; 2009-2010