Acute and long term effects of prenatal exposure to drugs of abuse

Estelle B. Gauda, M.D.
Professor of Pediatrics
Johns Hopkins Medical Institutions

Disclosures

I have no relevant financial relationships to disclose or conflicts of interest to release.

I will be discussing the off-label use of Clonidine.

Learning objectives:

Past month illicit drug use among people age 12 or older by state

National Survey on Drug Use and Health 2010

Illicit drug use

- 16% among pregnant teens and
- 7% among pregnant women 18–25 yrs
- AND
- 23% of pregnant women between 15–17 yrs of age abuse prescription drugs vs
- 13% in non-pregnant women

Rate of narcotic use per 1000 deliveries

Oxycodone/morphine/codeine/hydmorphone

5 fold increase over ~12 years

A few important definitions

- **Tolerance** – Loss of effect following repeated treatments such that a higher dose is required for equivalent effect
  - Caused by a complex interplay of cellular events that affects synapses and networks

- **Dependence** – Superactivation of cAMP systems
  - **Physical signs**: withdrawal (autonomic and somatic signs associated with drug absence)
  - **Psychological** – (addiction) – loss of control over drug use (impulsivity and compulsivity)
    - associated with reduced activity of the frontal cortex (hypofrontality)

**Neurocircuitry: Reward Pathway**

Dopamine Pathways

Serotonin Pathways

**Opioid Withdrawal**

Deficits in neurotransmitters systems

**Clinical Signs**

- **W** → Wakefulness
- **I** → Irritability
- **T** → Tremors, Temperature Instability, Tachypnea
- **H** → Hyperactive, High Pitch Cry, Hypertonia, Hyper-reflexia
- **D** → Diarrhea, Dysfunctional Suck and Swallow
- **R** → Rub Marks, Respiratory Distress, Rhinorrhea, Reflex
- **A** → Apnea, Alkalosis (respiratory), Acidosis (metabolic)
- **W** → Weight Loss
- **A** → Autonomic Dysfunction (sneeze, yawn, sweating)
- **L** → Laxation
Norepinephrine neurocircuitry in the brain mediates the physical signs of withdrawal leading to Elevated Sympathetic Output

HPAxis – CRF - ACTH – ADRENAIS-CORTISOL-EPI and NE

Increased vigilance
Alertness
Insomnia
Stress
Anxiety

Projections from
Efferents of Locus Coeruleus

Projections to
Afferents of Locus Coeruleus

Summation of cellular events: Acute responses to opiate exposure in a neuron in the LC

Effect of bath application of opiate antagonist (naltrexone) on the spontaneous firing rates of LC neurons from control and opiate exposed rats

Why not selectively target the LC neurons to decrease signs and symptoms of NAS?

Opioid and GABA receptors

HPA-CRF-ACTH – Adrenal glands – Cortisol and NE and EPI release

Upregulation of the cAMP pathway in opiate dependence

<table>
<thead>
<tr>
<th>Site of Regulation</th>
<th>Functional Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locus coeruleus (LC)</td>
<td>Physical Dependence and Withdrawal</td>
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<tr>
<td>Ventral tegmental area (VTA)</td>
<td>Dysphoria during early withdrawal</td>
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<tr>
<td>Periaqueductal gray</td>
<td>Dysphoria during early withdrawal Physical dependence and withdrawal</td>
</tr>
<tr>
<td>Nucleus accumbens (NA)</td>
<td>Dysphoria during early withdrawal</td>
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<tr>
<td>Amygdala</td>
<td>Conditioned aspects of addiction</td>
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<tr>
<td>Dorsal horn of spinal cord</td>
<td>Tolerance to opiate-induced analgesia</td>
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<tr>
<td>Myenteric plexus of gut</td>
<td>Tolerance to opiate-induced reduction in intestinal motility and increase in motility during withdrawal</td>
</tr>
</tbody>
</table>

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
    - (5.5mg increase - LOS by 1 day)
  - GA > 36 wks
  - Lower maternal weight at delivery
  - High infant BW
  - Benzodiazepines
  - SSRI exposure
  - Cigarette smoke 24 hrs prior to delivery

Genes and opioid addiction – the influence of polymorphisms

- The ABCB1 2677G/T/A, 1236CT, and 3435CT SNPs are highly prevalent (40%-50% in whites) and have been associated with methadone requirements in adults.
  - Regulates opioid absorption, distribution, and elimination

- The COMT 158AG SNP has a minor allele frequency of approximately 50% in whites and has been associated with responses to pain and morphine dosing requirements in adults.
  - Catechol-O-methyltransferase – that metabolizes catecholamines

- The OPRM1 118AG single-nucleotide polymorphism (SNP) has a minor allele frequency of 12% to 15% in whites and has been associated with an increased risk for addictive behaviors and variations in response to opioid medications.
  - OPRM1 – opioid mu1 receptor

Polymorphisms and NAS severity in term infants

Infants with the OPRM1 118AG AG/GG genotype
1) Shorter LOS by 8 days, mean (95% CI)
   - (8.5 days; 95% CI, 14.9 to 2.1 days; P = .009)
   - AA: LOS 24.1 days (19.8 to 28.4)
   - AG/GG: LOS 17.6 days (11.2 to 24.0)
2) Less likely to receive 2 or more medications (18% vs 56%; adjusted odds ratio, 0.76; 95% CI, 0.63-0.96; P = .006).

Infants the COMT 158AG AG/GG vs AA genotype had shorter LOS
1) Shorter LOS (-10.8 days; 95% CI, 18.2 to 3.4 days; P = .005)
   - Less likely to receive 2 or more medications (18% vs 56%)
   - adjusted odds ratio, 0.68; 95% CI, 0.83-0.96; P < .001).
2) Associations with the ABCB1 SNPs were not significant.

Withdrawal (toxicity) associated with in utero tobacco exposure

Prospective study:
- 27 nicotine exposed and 29 unexposed full-term newborn infants with no medical problems from comparable social class backgrounds, no other drug exposures
- NICU Neonatal Neurobehavioral Scale examiners blinded to treatment – performed with 48 hrs of birth
- Results:
  - Tobacco-exposed infants were more excitable and hypertonic, required more handling and showed more stress/abstinence signs, specifically in the central nervous system (CNS), GI, and visual areas. (all \( P < 0.05 \), exposed vs unexposed infants)

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

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  - Cigarettes smoke 24 hrs prior to delivery
- Decrease Severity
  - Breastfeeding/Rooming In
  - Quiet environments
  - Buprenorphine
  - Cocaine

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)

Cocaine

- Cocaine is a reuptake inhibitor of norepinephrine (NE), serotonin, and dopamine
  - Thereby increasing NE, serotonin and dopamine levels in the synapse
  - These neuromodulators bind to inhibitory and excitatory presynaptic and postsynaptic receptors
- The high associated with cocaine use:
  - heightened level of pleasure, increase in heart rate, blood pressure, insomnia,
Cocaine withdrawal is associated with decline in serotonin, dopamine and NE levels
Sleep, mood, attention, appetite, affect, heart rate, blood pressure

Onset Hrs to few days CRASH
• Exhaustion
• Hypersomnia
• No cravings to use
• Dysthymia
• Increased in appetite
• Restlessness
• irritability

Withdrawal 1–10 wks
Lethargy
Anxiety
Erratic sleep
Strong craving
Poor concentration

Emotional liability
Irritability
Depression
Cravings
Some dysphoria

Extinction up 28 wks

Cocaine withdrawal in infants

› Using the Brazelton Newborn Behavioral Assessment Scale

› Prenatal cocaine exposure
  - Increase irritability
  - Lability of state behavioral and autonomic regulation,
  - Poor alertness and orientation

Clinical Observation

› Infants prenatally exposed to cocaine alone do not require pharmacological therapy for “withdrawal syndrome” after birth

› Concurrent prenatal exposure to cocaine can reduce the severity of NAS from opiate exposure

Why?

Cocaine attenuates naloxone-precipitated opioid withdrawal in adult rats

Kosten. Life Sciences 1990; 47(18):1617-23

Cocaine attenuates naloxone-precipitated opioid withdrawal in adult humans

Kosten. Life Sciences 1990; 47(18):1617-23

Direct application of Cocaine to brain slices directly inhibits Activity from LC neurons

IV cocaine markedly reduces the activity of LC neurons in vivo

Cocaine exposure to embryonic LC (E14) neurons increases TNF-α in culture

Cocaine exposure to embryonic LC (E14) neurons leads to cell death mediated by TNF-α – activated apoptosis

Prenatal cocaine exposure inhibits neurite outgrowth of LC neurons but not of neurites in the substantia nigra
Summary findings: cocaine exposure in preclinical models of in utero exposure

- Apoptosis of LC neurons
- Less connectivity of LC neurons to targets – includes prefrontal cortex
- Alterations in D1/D2 and A2a signaling leading to phenotype that reduces neurogenesis and migration of neurons from the striatum to the cortex

Proposed Hypothesis

- Hyperactivity of LC neurons, mediated by upregulation of cAMP pathways substantially contributes to the physical withdrawal observed in adults and human infants. This effect is greatest with opiate exposure.
- Prenatal cocaine exposure is associated with decrease in number of LC neurons and connectivity in newborn animals
- Perhaps the “attenuated” physical withdrawal observed in infants prenatal exposed to cocaine may be secondary to less NE producing neurons in the LC secondary to cocaine toxicity to developing LC neurons.

Summary of brain and behavioral effects in newborn animals PCE

- Alterations in brain structure, signaling deficits in neurotransmitters systems
- Deficits in behavioral and cognitive function
  - Altered cognitive processes
  - Impaired attention; increased distractibility
  - Impaired spatial working memory,
  - Impaired ability to acquire new learning
  - Increased stress reactivity
  - Increased vulnerability to stressors

PCE and outcomes in humans

- Estimated effects of in utero cocaine exposure on language development through early adolescence –
  - Prospective longitudinal study, single site, 200 subjects in each group: 3, 5, and 12 year
- FINDINGS:
  - Dose-dependent, relationship between PCE level and expressive, receptive, and total language scores in the models controlling for age, child’s sex, and other prenatal drug exposures.
  - Regardless of prenatal cocaine exposures, adolescents from similarly disadvantaged backgrounds scored lower than average on a range of neurodevelopmental measures.
  - PCE-related impairments are reliably reported in sustained attention and behavioral self-regulation among school-aged children.

PCE and ADHD in children, and foster care is not protective

- Increase in symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder self-reported by the exposed children
- PCE children in adoptive or foster care were rated as having more problems with aggression, externalizing behaviors, and total behavioral problems than NCE children and CE children in maternal or relative care
  - 150 subjects in each group

Neurotoxicology and Teratology 33 (2011) 25-35
**SUBTYPES OF ADHD**

1. HYPERACTIVITY/IMPULSIVE
2. INATTENTIVE
3. COMBINATION

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**Prenatal cocaine exposure results in greater specific memory deficits in males than in female adult rats**


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**Neurobiology of attenuating effects cocaine exposure on NAS**

Similar biology that increases the risk of developing ADHD

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**NEUROBIOLOGY OF ADHD**

- Postsynaptic alpha2 receptors located on inhibitory interneurons in the cortex where their stimulation would disinhibit cortical neurons leading to cortical excitation (Andrews and Lavin, 2006).
- It is hypothesized that in ADHD there are less alpha2 receptors leading to hypostimulation of the PFC leading to easy distractability.
- Thus, alpha 2 agonist such as clonidine, will enhance activity at the alpha 2 receptor causing disinhibition leading to more cortical activation and attentiveness.
Depleting the Catecholamines within the slice (reserpine) blocks the excitatory effect of MPH (ritalin) on cortical neurons. Thus, pre-synaptic release of NE from LC in the slice is responsible for the supply of NE needed for cortical activation.


Regional Brain Morphometry and Impulsivity in Adolescents Following Prenatal Exposure to Cocaine and Tobacco

Participants: A total of 40 adolescent participants aged 13 to 15 years were recruited, 20 without PCE and 20 with PCE; a subset of each group additionally had tobacco exposure. Participants were selected and matched based on head circumference at birth, gestational age, maternal alcohol use, age, sex, race/ethnicity, IQ, family poverty, and socioeconomic status.

Results: After controlling for covariates, cortical thickness of the right dorsolateral prefrontal cortex was significantly thinner in adolescents following PCE (P=.03), whereas the pallidum volume was smaller in adolescents following prenatal tobacco exposure (P=.03). Impulsivity was correlated with thalamic volume following either PCE (P=.05) or prenatal tobacco exposure (P=.04).

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Jie Liu, PhD; Barry M. Lester, PhD; Nurunisa Neyzi, MS; Stephen J. Sheinkopf, PhD; Luis Gracia, PhD; Minal Kekatpure, MD; Barry E. Kosofsky, MD, PhD

Figure 2. Relationship between thalamic volume and sensation seeking Scale for Children (SSSC) score based on prenatal cocaine exposure (PCE); Brain/behavior association is shown as a solid line for PCE subjects (in solid circles, P = .05) and a dotted line for non-PCE subjects (open circles).

Figure 3. Relationship between thalamic volume and Sensation Seeking Scale for Children (SSSC) score based on prenatal tobacco exposure (PTE); Brain/behavior association is shown as a solid line for PTE subjects (in solid triangles, P = .04) and a dotted line for non-PTE subjects (open circles).

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Conclusion slide

- Schematic

Thank you for your attention