COCOAINE AND METHAMPHETAMINE: SHORT AND LONG TERM EFFECTS ON THE DEVELOPING BRAIN

Estelle B. Gauda, M.D.
Professor of Pediatrics
Senior Associate Dean of Faculty Development
Johns Hopkins Medical Institutions

Learning objectives:

- UNDERSTAND HOW COCAINE AND METHAMPHETAMINES HAVE ABUSE POTENTIAL
- UNDERSTAND WHY CONCURRENT EXPOSURE TO COCAINE AND OPIATES DECREASES THE SEVERITY OF NEONATAL ABSTINENCE SYNDROME
- UNDERSTAND MECHANISMS ACCOUNTING FOR THE ASSOCIATION BETWEEN PRENATAL STIMULANT EXPOSURE AND LATER DEVELOPMENT OF ATTENTION DEFICIT DISORDERS.

Predictors of severity of NAS

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

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

What drug exposures cause or contribute to withdrawal or delay transition

- Opiates: methadone, buprenorphine, heroin, prescription drugs: Vicodin, OxyContin, Percocet
- Stimulants: cocaine, methamphetamine, Caffeine
- Cannabinoids
- Tobacco
- SSRI

COCOAINE

- Cocaine is a reuptake inhibitor of norepinephrine (NE), serotonin, and dopamine
  - Thereby increasing NE, serotonin and dopamine levels in the synapse
  - NE, serotonin and dopamine then bind to inhibitory and excitatory presynaptic and postsynaptic receptors modulating activity of the neurons

Reviewed in CLINICAL OBSTETRICS AND GYNECOLOGY; 56, 186-192. Addiction. 2012 Nov;107
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
- Hypersominia
- No cravings to use
- Dysthymia
- Increased in appetite
- Restlessness
- irritability
- Lethargy
- Anxiety
- Erratic sleep
- Strong craving
- Emotional liability
- Irritability
- Depression
- Poor concentration
- Cravings
- Some dysphoria

Withdrawal 1–10 wks  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
- Infants prenatally exposed to cocaine alone do not require pharmacological therapy for “withdrawal syndrome” after birth

Clinical Observation

IN FACT –

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

Cocaine attenuates naloxone-precipitated opioid withdrawal in opiate dependent adult rats

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

IN FACT –

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

WHY
Cocaine is toxic to LC neurons

Direct application of cocaine to brain slices directly inhibits electrical activity from LC neurons

IV cocaine markedly reduces the activity of LC neurons in vivo

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

Projections of LC neurons
Depleting the catecholamines within brain slice (using reserpine) blocks the excitatory effect of methylphenidate (MPH) (ritaline) on cortical neurons. Thus, presynaptic release of NE from LC in the slice is responsible for the supply of NE needed for cortical activation.


Prenatal cocaine exposure reduces number of cells and inhibits neurite outgrowth - specific to LC neurons

Dey et al Neuroscience 139 (2006) 899–907

Cocaine exposure in preclinical models of in utero exposure

- Apoptosis of LC neurons
- Less connectivity of LC neurons to targets – includes prefrontal cortex
- Reduces neurogenesis and migration of neurons from the striatum to the cortex

Brain and behavioral effects in newborn animals with prenatal cocaine exposure (PCE)

- Alterations in brain structure, signaling deficits in neurotransmitters systems

  LONG TERM EFFECTS:

  - 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

Estimated effects of in utero cocaine exposure on language development through early adolescence

DESIGN:

- Prospective longitudinal study, Miami Prenatal Cocaine Study
  - 200 subjects in each group, 3, 5, and 12 years of age
  - Maternal interview, toxicology assays of maternal urine and infant urine, meconium.

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.


Jie Liu, Barry M. Lester, Nurunnisa Neyzi, MD, Stephen J. Shensko, MD; Luis Gracia, PhD; Minal Kekatpure, MD, Barry E. Kosofsky, MD, PhD

JAMA Pediatrics Vol 167 (No. 4), April 2013

(32 studies – Reviewed)
Summation of cellular events: Role of $\alpha_2$-noradrenergic stimulation during superactivation of cAMP systems induced by chronic opioid exposure

Clonidine increases cortical excitability in brain slices from rats (18–28 days) Increases NE tone in the PFC

Why clonidine is effective in treating individuals with ADHD

Neurobiology accounting for the attenuating effects cocaine exposure on NAS

Similar biology that increases the risk of developing ADHD in cocaine exposed infants

Target – LC neurons

Cocaine is toxic to developing LC neurons

Place holder for metamphetamine

Incidence across time and the United States

Place holder for metamphetamine

Mechanism of Action

Comparison with Cocaine
Place holder for methamphetamine

Physical, and Psychological Effects

Effects on the Fetus

Place holder for methamphetamine

Short and long term outcomes of infants and children prenatally exposed to Methamphetamine

---

**What I hope you learned today**

- Psychological “withdrawal” associated with excessive drug cravings and addiction is mediated by alterations in the Dopaminergic System in the VTA-NA-Prefrontal cortex, with secondary influence from the serotonergic system

- Physiological “withdrawal” - commonly seen as NAS in infants is predominately mediated by the superactivation of cAMP pathways leading to upregulation of NE and sympathetic output

---

**What I hope you will remember**

- Clonidine an alpha2 adrenergic receptor agonist is effective in the treatment of NAS and ADHD –

- NAS via inhibiting the LC neurons directly during NAS,

- ADHD by inhibiting inhibitory interneurons (GABA) in the basal forebrain leading to excitation- which increases attention.

---
THANK YOU FOR YOUR ATTENTION