Cocaine Inhibited Reuptake

- Cocaine
- NE Storage Granules
- Presynaptic Neuron
- Reuptake Pump (inhibited)
- Post Synaptic Neuron
- Norepinephrine
- Stimulated

Cocaine Inhibited Reuptake

Disclosure
- Consultant for Takeda Pharma.

Drugs of Abuse in Breastfeeding Mothers, New Research on Marijuana

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Cocaine Kinetics

- Highest concentrations in Urine and Kidney
- Oral bioavailability
  - Brain/blood ratio of over 20 is common. Highly concentrated in brain. Not present 6-8 hours after exposure.
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<table>
<thead>
<tr>
<th>Method of Administration</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>75 minutes</td>
</tr>
<tr>
<td>Oral</td>
<td>48 minutes</td>
</tr>
<tr>
<td>Intravenous</td>
<td>54 minutes</td>
</tr>
</tbody>
</table>

Cocaine in Breastmilk

- Little data are available, but there are possible toxic sequelae in breastfed infants when infant is breastfed too soon following maternal cocaine use.
- In one case a mother reported using 0.5 g of cocaine intranasally over 4 hours and breastfed her infant 5 times during this period. The infant became irritable with vomiting/diarrhea, and had difficulty focusing on the mothers face with dilated pupils. Three hours after the last breastfeed the infant was brought to ER for increased irritability. On examination the infant was tremulous, irritable, tachycardic, tachypneic and hypertensive with an increased startling response. The infants pupils were dilated with a poor response to light and reflexes were increased. Both Cocaine and its metabolite, benzoylecgonine, undoubtedly transfer into human milk. Other typical symptoms of cocaine intoxication.


What about Cocaine and Breastfeeding?

- Cocaine use should be strongly discouraged.
- NEVER, NEVER use topically on the nipple.
- Suggest a waiting period of at least 24 hours following last ingestion.
- Remove the infant from the environment.
- Even after waiting period, infant will likely receive significant amounts of benzoylecgonine via milk.
- Infant will probably test positive for Urine Drug Screens for days to weeks.
**LSD**

Lysergic Acid

- Produces CNS changes:
  - Visual illusions
  - Perceptual distortions
  - Synesthesia (overflow of sensory input so that colors are heard, and music becomes palpable)
  - Flashbacks and acute anxiety attacks can occur in heavy users.
  - Most potent of hallucinogens by weight.
  - Most subjects who use this drug retain their insight and recognize that what they see and hear is drug induced (differs from true schizophrenia, and amphetamine psychosis).
  - Has been used for centuries in religious rites.

**LSD**

- Usual dose is 100 micrograms.
- Onset occurs 40-90 minutes post ingestion.
- Duration of hallucinations is 8-12 hours.
- Physiologic effects include:
  - Mydriasis, tachycardia, hyperglycemia, piloerection, slight fever, salivation, lacrimation, tremor, hyperreflexia, nausea, vomiting, hyperactivity.
- Other side effects:
  - Is not a human teratogen, nor carcinogenic.
  - Death from LSD exposure is not due to drug, but suicide or accidental trauma.

**LSD and Breastfeeding**

- No data are available.
- Transfer into MILK and Oral absorption in infant is likely due to:
  - Small molecular weight of LSD
  - Good oral absorption
  - Minuscule dose required (microgram)
- Heavy users should not breastfeed.
- Occasional users should pump and dump for minimum of 24-48 hours post ingestion ??????

**Phencyclidine (PCP)**

- Phencyclidine (PCP)
  - Angel dust, killer weed, crystal, elephant tranquilizer, etc.
  - Well absorbed, oral bioavailability ~ 72%, Vd ~ 6.2 L/Kg
  - Half-life ~ 24-51 hours, must be metabolized first, and then excreted…may have extremely long T1/2 in infants.
  - Drug Screens positive in Adults for 2-4 weeks. Probably much longer in infants.
  - Side effects are enormous including: coma, catatonic syndrome, hallucinations, violent behavior.
  - PCP is extremely dangerous, and women should not breastfeed following its use for long periods (perhaps weeks).
Opiates/Opioids

- **Natural Substance is:** Morphine
- **Synthetic Derivatives:**
  - Heroin, Hydromorphone, Oxymorphone, Hydrocodone
- **Meperidine and Congeners**
  - Meperidine, Pethidine, Diphenoxylate (Lomotil),
  - Fentanyl, Loperamide (Imodium)
- **Methadone and Congeners**
- **Others:** Butorphanol (Stadol), pentazocine (Talwin), naltrexone (Trexan), naloxone (Narcan), nalbuphine (Nubain), Tramadol.

### Morphine/Heroin & Breastfeeding
- Addicts may use enormous doses of these medications, and hence milk levels could be much higher.
- Concentration ranges as high as 0.5 mg per liter. Realistically, 50-60 µg/Liter is most likely.
- Few untoward effects have been noted at normal doses
  - These are not the doses potentially used by addicts.
- Poor oral bioavailability (< 25%), due to sequestration in the infant’s liver limits systemic levels in infant.
- Heroin is metabolized to morphine in minutes.

### Methadone
- Opioid with long half-life
- Half-life ~ 13-55 hours
- Methadone is a potent and very long-acting opiate analgesic. It is primarily used to prevent withdrawal in opiate addiction.
- In 12 breastfeeding women on methadone maintenance doses ranging from 20-80 mg/day, the mean concentration of methadone in milk was 116 (72-160) µg/L respectively. This equates to a mean of 2.79% of the maternal dose per day.
- Excellent study of 8 women with doses of 40-105 mg/d
  - Relative infant dose ~ 2.8%
Methadone

- Now approved by AAP for use in Breastfeeding mothers (2001)
- Higher doses such as 80-120 mg/day reduce the addicts’ use of heroin by reducing the euphoria of heroin. Lower doses do not.
- At higher doses, caution is recommended. Observe for sedation.
- Recent call at 600 mg/day dose?
- Withdrawal in newborn infants is slow and generally starts about 3-4 days.
  - Symptoms include: hyperactivity, tremors, hypotonia, jitteriness.

Fentanyl

- Gaining in popularity and death rate
- Standard Epidural opioid (35-50 micrograms)
- Super Potent (50-100 times more than morphine)
- Relatively short half-life (2-4 hours)
- RID (35-100 µg) = 2.5% - 5%
- Main risk is POTENCY, and DOSE used by addicts.

Other Opiates Used and Abused

- Hydrocodone
  - Potency (1.5-2 X morphine)
  - Subject to metabolism, but still good choice.
- Oxycodone
  - Potency (1.5-2 X morphine)
  - Significant euphoria
  - Highly addictive
- Fentanyl
  - Potency - 80-100 X morphine
  - Rapid onset, short half-life
- Buprenorphine
  - Subutex

Hydromorphone (Dilaudid)

- Not metabolized to more potent metabolite
- Potency (7-10 X morphine)
- Caution in breastfeeding mothers
- RID = 8.67%
- Following dose of 4 mg q 4 h respiratory depression in 6 day old breastfed infant. Naloxone recovery.

Hydromorphone (oral)

- Potency: 2.5-4
- Caution in breastfeeding mothers
- RID: 0.67%
- Dose in 4 mg q 4 h, respiratory depression in 6 day old breastfed infant. Naloxone recovery.

Equivalency of Opiate Drugs

<table>
<thead>
<tr>
<th>Analgesic Drug Name</th>
<th>Strength</th>
<th>Equivalent Dose</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>1000 mg</td>
<td>3600 mg</td>
<td>63-89%</td>
</tr>
<tr>
<td>Ibuprofen[7]</td>
<td>400 mg</td>
<td>2220 mg</td>
<td>87-100%</td>
</tr>
<tr>
<td>Codeine</td>
<td>100 mg</td>
<td>180 mg (PO)</td>
<td>~90%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100 mg</td>
<td>200 mg (IR), 50 mg (ER)</td>
<td>62-70%</td>
</tr>
<tr>
<td>Morphine (oral)</td>
<td>100 mg</td>
<td>180 mg (PO)</td>
<td>80%</td>
</tr>
<tr>
<td>Oxycodone[15]</td>
<td>10 mg</td>
<td>6.67 mg</td>
<td>0.87</td>
</tr>
<tr>
<td>Morphine (IV/IM)</td>
<td>3 mg</td>
<td>3.33 mg</td>
<td>100%</td>
</tr>
<tr>
<td>Morphine (IV/IM)</td>
<td>8 mg</td>
<td>2.5 mg</td>
<td>62%</td>
</tr>
<tr>
<td>Methadone (acute)[19]</td>
<td>4-16 mg</td>
<td>3.33 mg</td>
<td>85-90%</td>
</tr>
<tr>
<td>Methadone (chronic)[19]</td>
<td>2-8 mg</td>
<td>1.1 mg</td>
<td>85-90%</td>
</tr>
<tr>
<td>Hydrocodone (oral)</td>
<td>4 mg</td>
<td>15 mg, 5 mg (PO)</td>
<td>60%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.5 mg</td>
<td>4 mg (PO)</td>
<td>40%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50-100 mg</td>
<td>85 mg (IV, 10 mg IM)</td>
<td>5% (RI), 45% (TD)</td>
</tr>
</tbody>
</table>
Amphetamines/Methamphetamines

- Amphetamines in general are small molecules (368 daltons), have high affinity for CNS, and are extremely potent.
- Amphetamines are strong CNS stimulants that last longer than cocaine.
- Milk/Plasma ratio is high 2.8-7.5….although untoward effects have not been reported, yet. RID=1.8-6.9%
- Excitement, anorexia, insomnia, hypertension are possible.
- Many Diet Pills are cousins of the amphetamines.
- Methylphenidate (Ritalin) probably safe….RID=0.4%

Methamphetamine

- Methods: Study of 33 women. Pharmacokinetic data from 2 women were analyzed.
- The half-life values for MA in the breast milk were 11.3 and 40.3 hours.
- The absolute infant doses were 21.3 and 51.7 µg/kg/day.
- Methamphetamine disappears from breast milk approximately 1 day before the maternal urine MA becomes negative.
- Conclusion: Breastfeeding can be safely initiated in mothers whose urine MA screen has turned negative for ≥ 24 hours.
- However, concurrent maternal substance use treatment and screening is necessary for continued promotion of lactation.


Hallucinogenic Amphetamines

- MDMA=Adam, Ecstasy
  - MDM=XTC, Essence; MDEA=Eve; MDA=Harmony, Love, Love Drug
- All of these agents are amphetamine derivatives, with extreme hallucinogenic and stimulant activity. Half-lives = < 8 hours.
- Duration of action
  - 4-6 hours with doses of 75-150 mg.
  - Hallucinations, extreme agitation and seizures in infants possible.
- Recommend pumping and discarding for 24-48 hours. Again this depends on the dose administered.

Flakka

(Alpha PVP)

- Cousin of the amphetamine-like Canthinone
- Excited delirium, euphoria, enhanced alertness, increased hyperactive movements, hyperthermia
- Like bath salts, extreme VIOLENT behavior is common.
- Cheap and easy to get.
- May be active ingredient in bath salts
Alcohol

- Alcohol has a Milk/Plasma ratio of 1. It readily exchanges with milk and plasma.
- One report suggests reduction of 23% in milk intake.
- Due to alcohol effect on Oxytocin release.
- Reduction of letdown has been reported, but dose was high (1-2 gm/Kg).
- Maternal blood levels of 300 mg% must been attained before significant side effects are reported in infant.
- Avoid breastfeeding for up to 2-3 hours.
- Mom can probably breastfeed after moderate use as soon as she feels normal (about 2 hours).

Synthetic Marijuana “K2” or “Spice”

- NOT Cannabis or Marijuana
- HIGH POTENCY man-made psychoactive products containing one or more synthetic cannabinoids sprayed onto an herbal substrate
- Other names: K2, fake weed, Yucatan Fire, Skunk
- K2 consists of Synthetic CB1 agonists similar to Δ9-THC but were synthesized years ago as experimental agents.
- They act on Cannabinoid receptors: CB1 receptor similar to THC
- High-potency, high-efficacy, cannabinoid receptor full agonists
- Side Effects: tachycardia, vomiting, agitation, confusion, hallucinations, dangerous hypertension, heart attach.
- Treatment: Lorazepam, diphenhydramine, haloperidol.

Synthetic Marijuana “K2” or “Spice”

- Undetectable in urine or serum drug screens.
- Use in increasing rapidly.
- Variable and unpredictable toxicity of new compounds
- Points to remember:
  - SPICE IS NOT MARIJUANA
  - IT IS NOT SAFE, BUT EXCEEDINGLY DANGEROUS
  - RAGE IS COMMON
  - CHECK FOR RHABDOMYOLYSIS AND RENAL DAMAGE, SEIZURES, CARDIAC ARRHYTHMIAS.

Marijuana
CB1 receptors (CB1R) and CB2 receptors (CB2R).
- CB1Rs are expressed primarily in the brain and are responsible for the psychoactive effects of cannabinoids.
- CB2 receptors are localized primarily in the periphery on immune cells where they mediate the immunomodulatory effects of cannabinoids.
  - Moderate peripheral neuropathic pain

Endocannabinoids
- Anandamide
- 2-Arachidonyl Glycerol
  - Similar to THC but no psychoactive effects
  - Analgesia
  - Antinauseant
  - Enhanced appetite
  - Blocks the CB1 receptors STOPS breastfeeding in rodents

Cannabis (marijuana)
- Has been used for 6000 years.
- Perceived to be harmless, but it may not be!
- Used in 15% of pregnancies today
- New data suggests cannabis during gestation is a potential teratogen.
- Evidence of damage to the mesocorticolimbic, hippocampus, and cerebellum is growing
- Prenatal cannabis use may be associated with cognitive, behavioral, and neuropsychiatric deficits. Data in animals is strong.
- OLD Milk/Plasma ratio ~ 8 is probably wrong. OLD Breastmilk data is worthless.
- Cannabis is known to suppress Prolactin, and reduces Oxytocin release in animal models (due to CB1 blockade).
Diseases Presently being treated with Cannabis

- Anorexia
- Emesis
- Neuropathic pain
- Inflammation
- Multiple sclerosis
- Neurodegenerative disorders (Parkinson’s disease, Huntington’s disease, Tourette’s syndrome, Alzheimer’s disease)
- Epilepsy
- Glaucoma
- Osteoporosis
- Schizophrenia
- Cardiovascular disorders
- Cancer
- Obesity
- Metabolic syndrome-related disorders

Individual Important Components

1) Tetrahydrocannabinol (THC) Delta-9-THC
   - 11-Hydroxy THC
     - Psychoactive component of Cannabis.
     - Activate CB1 receptors in brain
   - 11-Nor-9-carboxy THC (THC-COOH) (inactive)

2) Cannabidiol (CBD)
   - Non-psychoactive
   - Actually counteracts psychoactive impairment from THC.
   - Does not act at CB1 or CB2
   - Acts at GPR55 (cannabinoid receptor) and 5-HT1a receptors instead

Cannabidiol (CBD)

- Natural, Non-psychoactive constituent of Cannabis
- Does produce:
  - Neuroprotection
  - Anticonvulsant: treatment-resistant epilepsy (Dravet syn, Lennox-Gastaut syndrome.
  - Analgesia
  - Anti-emetic
  - Anti-spasmodic
  - Anti-inflammatory effects
  - Anti-anxiety
  - May be useful for autoimmune diseases.
  - “May” be useful for Schizophrenia, anxiety, substance abuse.
- Does not produce psychoactive properties...less powerful

Metabolism of Δ⁹ THC

- More than 100 metabolites have been identified.
- Apparently, all tissues metabolize THC to some degree
- Most Important are:
  - 11-Hydroxy THC (active)
  - 11-Nor-9-carboxy THC (THC-COOH) (inactive)
- Levels of metabolites depend on
  - Type of ingestion, oral, smoked, transcutaneous, rectal
- Within 5 days, 80-90% of THC is excreted, mostly as metabolites.
  - 65% in feces
  - 20% in Urine

Huestis MA. Human cannabinoid pharmacokinetics. PubMed PMID: 17712819
Marijuana Kinetics

- Terminal Elimination. Half-life = 4.3 days (range, 2.6-12.6 days)
- Content of marijuana cigarettes is highly variable…content varies enormously.
- Absorption:
  - Inhaled = 10-56%  Peak = 7-8 minutes
  - Oral absorption = 90-95%  Peak = very slow (1-2 hrs)
  - Most metabolized…real plasma levels < 10%
  - Huge Volume of Distribution (adipose tissue)
- Passive absorption is minimal but evident.
- Plasma levels drop rapidly to 10% of peak in 3-4 hours and are generally < 1 ng/mL.

Absorption (Smoking)

- Rapid absorption, more addicting
  - Lungs to brain absorption rapid
  - Bioavailability:  2 – 56%
    - Highly Variable absorption even when accurately controlled by computer.
    - Variable smoking techniques probably in population
    - Due to uncertainty of dose
    - Function of number, duration and spacing of puffs, hold time and depth of inhalation.
- Average Plasma Peak approximately 100-200 ng/mL.
- With THC≈1.75% to 3.55% (1980’s) mean plasma levels = 7-18 ng/mL after one puff.  After 1 cigarette = 150 ng/mL.
- Within 2 hours levels were < 5 ng/mL.
**ORAL Dronabinol (Pure THC)**

![Graph](image)

**Absorption (Intravenous)**
- Dose = 2.5 and 5 mg IV
- Plasma levels = 82 and 119 ng/mL
- Some subjects withdrew from study
  - Paranoia
  - Panic
  - Hypotension
  - Acute paranoid reaction
  - Schizophrenic-reaction
- These studies suggest that CNS CB1 CB2 receptors could be involved in psychotic disorders.

*D’Souza 15173844*

**Urine Concentrations of THC Metabolites**

![Graph](image)

**Oral Absorption**
- Few studies available.
- Absorption is Much slower
- Bioavailability reportedly = 6-20%.
  - Lower absorption, metabolism in gut, first pass effect, pharmacologic effect is "extended", onset delayed.
- Dose = 10-15 mg oral
- Peaks ranged from 4.4 to 11 ng/mL
- $C_{max}$ occurs at 1-5 hours following ingestion of 20 mg
- Slow rate of absorption and lower THC levels in plasma
  - But Plasma levels last MUCH MUCH longer as compared to smoking
- Paranoia
- Panic
- Hypotension
- Acute paranoid reaction
- Schizophrenic-reaction
- These studies suggest that CNS CB1 CB2 receptors could be involved in psychotic disorders.

1. Ohlsson 6207706
2. Buntie 1207857, Meir 9157827
Distribution of THC

- Plasma levels decrease rapidly due to DISTRIBUTION to peripheral fatty tissues and metabolism in liver
- THC is HIGHLY lipophilic (loves fat)
- Initially found in highly perfused tissues
  - Lung, heart, brain (1%), liver
- Subsequently
  - Fat/Brain ratio = 21:1 after 7 days exposure
  - Fat/Brain ratio = 64 after 27 days exposure.
  - May be sequestered in CNS

Dronabinol (Marinol)

- Synthetic delta 9 THC
- 2 mg, 5 mg, 10 mg capsules
- Usually taken orally, can be used rectally
- Slower absorption (90-95% absorbed)
- ONLY 10% is systemically available
- Initial T1/2 = 4 hr. Terminal T1/2 = 25-36 h
- Duration = 4-6 hours
- Bioavailability is HIGHLY variable via oral route
  - Depends on vehicle and physiological facts
  - Absorption and rates of metabolism
- Indications: Anorexia, N/V cancer chemotherapy, those who’ve failed typical antiemetic therapy

Breastmilk Studies

- Small to moderate secretion of THC in breastmilk has been documented.
- Mother who smoked Cannabis once daily for 7 months, up to 105 µg/L of THC was quantified in her milk.1
  - Her infant had negative urine samples and was reported to have normal development by the pediatrician.
  - Another Mother who used Cannabis 7 times per day for 8 months was found to have 340 µg/L of THC.
  - In her second milk sample she had 60.3 µg/L of THC. M/P ratio = 8 ???
    - Her infant had negative urine samples but positive fecal samples for 347 ng of THC. This infant was also reported to have normal development by the pediatrician.
  - Another mother using unknown amount had 86 µg/Liter milk.2

Suggestions

- If mother is drug screen positive for MARIJUANA at birth:
  - Advise strongly against further use in breastfeeding
  - Advise it might lower her infant’s IQ.
  - Advise it will MIGHT lower her milk supply.
  - But allow BREASTFEEDING the infant.
  - IQ deficits may be offset by Breast Milk (theoretical)

- Suggest to clinician that the infant be tested at one month for cannabis.

What do you tell the Mom?

- If mom is pregnant, WARN her against alcohol and marijuana.
- If mom is multi-drug user (cocaine, methamphetamine, phencyclidine), advise against breastfeeding.
- If mom has delivered and Mom is drug-screen positive for MJ:
  - WARN her not to use it again. Let her breastfeed.
  - Suggestion: Bring the infant back at one month and do drug screen on infant.
- Do not recommend breastfeeding in persistent, untrustworthy mother.

Recommendations for women wishing to breastfeed

- Antenatal assessment of mental health and parenting and breastfeeding ability
- Factors favoring breastfeeding include early engagement in antenatal care and in substance use intervention.
- Urine drug screen(s) may assist clinical decisions
  - Remember, drugs screens may be positive 2-5 days after use.
  - Remember that positive drug screens do NOT mean levels are clinically relevant !!!!!
- May predispose some patients to disengage from postpartum/neonatal care.
- Regular assessment at scheduled appointments are good indication of patient compliance.
- Retention in substance abuse treatment is important due to chronic relapsing nature of substance abuse.
- A support network is critical. Both professional and social.
- If patient continues positive for Methamphetamine, etc. use, discontinue breastfeeding.
- Notify child protection service.

References