Pharmacology of Opioid Agonist Treatment (OAT): Methadone and Buprenorphine as the Standard of Care in Pregnancy

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Disclosures

- No financial relationships or duality of interest to disclose
- I will be discussing off-label use of agents (methadone and buprenorphine)
Learning Objectives

Demonstrate an understanding of the pharmacologic differences between methadone vs buprenorphine in the treatment of opioid use disorder in pregnancy

Compare maternal and neonatal outcomes identified with the use of methadone vs buprenorphine in the treatment of opioid use disorder in pregnancy

Determine the most effective opioid agonist treatment (OAT): methadone vs buprenorphine that should be used to treat opioid use disorder in pregnancy in your community
The prevalence of opioid use among pregnant women ranges from 1–2% to as high as 21%.

Methadone maintenance has been the treatment of choice for opioid-dependent women since the 1970s.

Buprenorphine

Prenatal methadone or buprenorphine exposure may result in neonatal opioid withdrawal syndrome.
Opioid Epidemic: The FACTS

The amount of opioids prescribed per person was three times higher in 2015 than in 1999.

30–60 MME = hydrocodone 5–10 mg po q 4 hours
90 MME = hydrocodone 15 mg q 4 hours
120 MME = hydrocodone 20 mg q 4 hours

Opioid Epidemic: Impact on Women’s Health

- In just one decade, deaths from prescription painkillers (opioids) rose by more than 400% among women. (CDC, 2013)
- Every 3 minutes, a woman goes to the emergency room for prescription painkiller misuse. (CDC, 2013)
- The number of drug overdose deaths has never been higher, and the majority of these deaths (more than 6 out of 10 in 2014) involved opioids. (CDC, 2015d)
- At least half of opioid deaths involve a prescription opioid. *When pregnant women use opiates, the fetus can also become dependent on them.* (CDC, 2016d)
Active metabolites enter the CNS of the fetus causing neuronal cell injury or death

Studies have shown physiologic brain changes

Impact on cognitive and behavioral development

Side effects of certain drugs can cause vasoconstriction and decrease blood supply

Result in complications of pregnancy (placental abnormalities, IUGR, preterm delivery)

Drug abuse or chronic drug use can increase risk for NAS
# Prenatal Drug Exposure: Potential Effects on Birth and Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Tobacco</th>
<th>Marijuana</th>
<th>Stimulants</th>
<th>Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy complications</td>
<td>No fetal growth effects</td>
<td><strong>Cocaine</strong></td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Prematurity</td>
<td>No physical abnormalities</td>
<td>Prematurity</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Decreased birth weight</td>
<td></td>
<td>Decreased birth weight</td>
<td>Decreased birth weight</td>
</tr>
<tr>
<td>Decreased birth length</td>
<td></td>
<td>Decreased birth length</td>
<td>Decreased birth length</td>
</tr>
<tr>
<td>Decreased birth head circumference</td>
<td></td>
<td>Decreased birth head circumference</td>
<td>Decreased birth head circumference</td>
</tr>
<tr>
<td>Sudden infant death syndrome (SIDS)</td>
<td></td>
<td>Intraventricular hemorrhage</td>
<td>Fetal and neonatal abstinence syndrome</td>
</tr>
<tr>
<td>Increased infant mortality rate</td>
<td><strong>Methamphetamine</strong></td>
<td></td>
<td>Sudden infant death syndrome (SIDS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small for Gestational Age (SGA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased birth weight</td>
<td></td>
</tr>
</tbody>
</table>
## Prenatal Drug Exposure: Potential Effects on CNS Development, Cognitive Function, and Behavior

<table>
<thead>
<tr>
<th>Tobacco</th>
<th>Marijuana</th>
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<th>Opiates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed maternal-infant interaction</td>
<td>Mild withdrawal symptoms</td>
<td><strong>Cocaine</strong></td>
<td>Abstinence syndrome</td>
</tr>
<tr>
<td>Excitability</td>
<td>Delayed state regulation</td>
<td><em>Neonatal/Infancy</em></td>
<td>Less rhythmic swallowing</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>Reading, spelling difficulty</td>
<td>Early neurobehavioral deficits: orientation, state regulation, autonomic</td>
<td>Strabismus</td>
</tr>
<tr>
<td>Stress abstinence signs</td>
<td>Executive function impairment</td>
<td>stability, attention, sensory, and motor asymmetry, jitteriness</td>
<td>Possible delay in general cognitive function</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>Early tobacco and marijuana use</td>
<td>Poor clarity of infant cues during feeding interaction</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Reduced IQ</td>
<td></td>
<td>Delayed information processing</td>
<td>Aggression</td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td>General cognitive delay</td>
<td>Feelings of rejection</td>
</tr>
<tr>
<td>Antisocial behavior</td>
<td></td>
<td></td>
<td>Disruptive/inattentive behavior</td>
</tr>
<tr>
<td>Impulsivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use and dependence</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Methamphetamine                             | Poor movement quality (3rd trimester exposure)                            |                                                                          |                                                                          |
|                                              | Low arousal                                                              |                                                                          |                                                                          |
|                                              | Increased lethargy                                                       |                                                                          |                                                                          |
|                                              | Increased physiologic stress                                             |                                                                          |                                                                          |
|                                              | No mental or motor delay                                                 |                                                                          |                                                                          |

*Effects may be subtle and transient

Pharmacology and Pharmacokinetics Properties of Methadone vs Buprenorphine and other Opiates
Comparison of Opiate Drugs

Derived fully or partially from Opium

- Codeine
- Heroin
- Hydromorphone
- Hydrocodone (Vicodin™, Lortab™, Norco™)
- Oxycodone (Percocet™, Oxycontin™)
- Fentanyl
- Methadone
- Meperidine (Demerol™)
- Buprenorphine (Subutex™) – agonist/antagonist
Structural Characteristics
Methadone vs other Opiates

morphine

[Diagram of morphine]

heroin

[Diagram of heroin]

methadone

[Diagram of methadone]

codeine

[Diagram of codeine]
Structural Characteristics
Buprenorphine vs other Opiates

morphine

heroin

Buprenorphine

codeine
# Opiate Metabolism

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Receptor binding</th>
<th>Routes of administration</th>
<th>Metabolic pathway</th>
<th>Ceiling dose</th>
<th>Onset of effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>(\mu, \kappa) (weak)</td>
<td>Oral tablet, oral liquid, intramuscular or subcutaneous, epidural or intrathecal, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>NA</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>(\mu, \kappa)</td>
<td>Oral</td>
<td>CYP2D6</td>
<td>Yes for combination products, no for pure hydrocodone</td>
<td>Rapid</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>(\mu, \kappa) (strong)</td>
<td>Oral, rectal</td>
<td>CYP3A4, CYP2D6</td>
<td>Yes for combination product, no for pure oxycodone</td>
<td>Rapid</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>(\mu) (agonist), (\kappa) (agonist, weak partial)</td>
<td>Transdermal, transmucosal</td>
<td>CYP3A4, glucuronidation</td>
<td>Yes</td>
<td>Slow</td>
<td>Long</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>(\mu, \kappa) (weak), (\delta) (weak)</td>
<td>Oral, intramuscular or subcutaneous, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>N/A</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Oxyomorphine</td>
<td>(\mu)</td>
<td>Oral, intravenous, rectal</td>
<td>Glucuronidation</td>
<td>None</td>
<td>N/A</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>(\mu, \kappa, \delta)</td>
<td>Oral</td>
<td>Glucuronidation</td>
<td>6–12 mg/d</td>
<td>Rapid</td>
<td>Long</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>(\mu, 5-HT, NE)</td>
<td>Oral</td>
<td>Glucuronidation</td>
<td>500 mg/d</td>
<td>Slow</td>
<td>ER or IR</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>(\mu, \kappa) (weak)</td>
<td>Transdermal, transmucosal, intranasal, intravenous</td>
<td>CYP2C9 (minor), CYP3A4</td>
<td>None</td>
<td>Very rapid (transmucosal, intravenous)</td>
<td>Very short</td>
</tr>
<tr>
<td>Methadone</td>
<td>(\mu, \kappa) (weak), (\delta) (strong), NMDA</td>
<td>Oral</td>
<td>CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2C9</td>
<td>None</td>
<td>Very slow (transdermal)</td>
<td>Very long (transdermal)</td>
</tr>
</tbody>
</table>

Drugs Used to Treat Opioid Use Disorders

- Methadone
- Buprenorphine (Subutex™)
- Buprenorphine + naloxone (Suboxone™)
- Naltrexone (Revia™)
Drug Transfer Across the Placenta

- Transfer occurs
  - passive diffusion
  - protein transport
- Transfer dependent
  - Molecular size (<500)
  - pH
  - Protein binding
  - Lipid solubility
Opiates Considerations in Pregnancy

- Opiate drugs are highly lipophilic and have relatively low molecular weights
  - Cross the placenta by simple diffusion from mother to fetus
  - Tend to accumulate in the fetus
  - Longer half-life in the fetus (enzymes of glucuronidation and oxidation not fully developed, immature renal function)

- Babies at increased risk of low birth weight and poor growth. May have smaller head size and be born pre-term

Chasnoff, NeoReviews 2003
Goal of Opiate Agonist Treatment (OAT) in Pregnancy

- Improve outcomes for mother and baby
  - Minimize prenatal risks
  - Increase participation in prenatal care
  - Minimize opiate withdrawal
  - Decrease illicit drug use
  - Assist mother in transition to a safe and stable lifestyle
Comparison of Methadone/Buprenorphine Use in Pregnancy and NAS
C–II narcotic (opioid) μ receptor agonist

a “substitute” for opiate drugs of abuse – heroin

produces similar effects and reduces withdrawal symptoms
Methadone Available Dosage Forms

- 40 mg dispersible tab – must be dissolved in water/juice
- 5 and 10 mg regular tablets
- 1 mg/ml or 10 mg/ml concentrate – note: concentrate must be mixed in water/juice
Methadone – Pharmacology

- Bioavailability = 80–95%
- $T\frac{1}{2} = 15–55$ hours
- Does not create euphoria, sedation, or analgesia
- Endpoint: cravings stop
- Establish individualized dosing
- Usually require 60 to 120 mg/day
Methadone: Side Effects

- Long t½ may result in overdose
- Potential for apnea, respiratory failure, seizures
- Be aware of multiple drugs that can potentiate effects
- Other: sweating, constipation, weight gain, urinary retention
- Caution: Noncardiogenic pulmonary edema has resulted from therapeutic doses
Methadone Effects on Pregnancy

- Accelerated clearance in 3rd trimester
- Increase doses often required as gestation nears term
- Divided daily doses may keep maternal plasma levels stable
- Enhances fetal growth

Anderson IB et al. Use of Methadone. WJM, 2000; 172: 43
Methadone Effects on Baby

- Crosses the placenta
- Does not cause fetal abnormalities
- Not associated with premature and LBW
- Infant can be weaned (if needed)
- Capatible with breastfeeding

Buprenorphine

➢ C–III narcotic (opioid) agonist/antagonist (partial μ agonist and K antagonist)
➢ High affinity for μ opioid receptors
➢ Less abuse potential than methadone
➢ Rx can be filled by regular pharmacy (covered by insurance)
Buprenorphine
Available Dosage Forms

- **C–III narcotic**
- **Subutex®** = buprenorphine
  2 mg and 8 mg sublingual tablets
  brand names: Belbuca® buccal film,
  Butrans® transdermal patch,
  Sublocade® prefilled subQ syringe,
  Probuphine® subQ implant kit,
  Buprenex® injection
- **Suboxone®** = buprenorphine
  + naloxone 2 mg/0.5, 4 mg/1,
  8 mg/2, 12 mg/3 sublingual tabs
  or sublingual/buccal film
  brand names: Bunavail® film or Zubsolv® tab
C–III narcotic

Buprenex® injection is NOT INDICATED FOR TREATMENT OF OPIATE ADDICTION!!!!

Buprenex® injection is indicated for the treatment of pain!

Injection used to compound neonatal buprenorphine oral solution 75 mcg/ml
Buprenorphine (Subutex™)
Buprenorphine/Naloxone (Suboxone™)

- FDA approved 2002
- Treatment of opioid addiction
- Relieves withdrawal, reduces cravings, and blocks the effects of heroin and other opiates
- Bioavailability (sublingual) = 30–40%; t ½ = 37 hours
- Peak concentrations 30–60 mins after sublingual dose
- Maintenance doses: 12 to 32 mg/day (sublingually) **equivalent to 30–70 mg oral methadone**
- Doses must be individualized (like Methadone)
- Suboxone™ – contains naloxone (hard to overdose)
Buprenorphine (Subutex™)  
Buprenorphine/Naloxone (Suboxone™)

➢ Prescribers must be “trained”
➢ Internet or one day course
➢ A directory of prescribers can be found at

http://buprenorphine.samhsa.gov/bwns_locator

➢ Almost 14,000 physicians have been authorized to prescribe

➢ REMS Program
   ➢ Subutex sublingual film: Medication Guide sheet
     ➢ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020732s018lbl.pdf#page=27
   ➢ Suboxone sublingual film: Medication Guide sheet
     ➢ http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022410s026s027lbl.pdf#page=30

Reckitt and Benckiser Pharmaceuticals, Inc.  Product Info, 2007
Buprenorphine Effects on Pregnancy

- Limited experience in pregnancy
- Women must be willing to take med
- Minimal side effects (sedation) following a dose
- Fewer drug–drug interactions
- Less chance for overdose
Buprenorphine Effects on Baby

- Crosses the placenta
- Less frequent NAS
- Symptoms of NAS may be less severe
- Fetal risk not greater than methadone
- Compatible with breastfeeding

Methadone versus Buprenorphine
OAT in Pregnancy

- Few controlled trials comparing methadone and buprenorphine
- Most case series or small comparative trials
- Results often confounded by
  - Cigarette smoking
  - Other substance abuse
  - Psychiatric disorders
  - Lack of prenatal care
Methadone and Buprenorphine

➢ NOT FDA approved
➢ Methadone is considered standard of care
➢ Buprenorphine shows promise
➢ Both are Pregnancy Category C
➢ Opiate antagonists are NOT recommended
➢ Pharmacotherapy should be used with psychosocial support
Buprenorphine OAT in Pregnancy

- Those whom benefits outweigh risk
- Lack of access to a methadone clinic
- Those who do not tolerate methadone
- Those who refuse methadone treatment
- Women who become pregnant while on therapy should stay on it
- Women on buprenorphine + naloxone (suboxone) should be switched to buprenorphine (subutex) alone
Maternal Opioid Treatment: Human Experimental Research ‘MOTHER’ Study

- Randomized, double-blind controlled trial that compared methadone-exposed neonates vs buprenorphine-exposed neonates
- Similar maternal treatment and delivery outcomes between the medications
- Compared to methadone-exposed infants, buprenorphine-exposed infants:
  - Required 89% less morphine to treat NAS
  - Spent 43% less time in the hospital
  - Spent 58% less time in hospital being medicated for NAS
- NAS treatment rates did not differ significantly between the groups
- Women on buprenorphine were more likely to discontinue treatment (28/86 vs 16/89)

Maternal Opioid Treatment: Human Experimental Research ‘MOTHER’ Study

Methadone vs Buprenorphine
Lactation Considerations
Drug Factors Favoring Transfer

- Unionized state
- High lipid solubility
- Low protein binding
- Weak base
- Low molecular weight
- Maternal serum concentrations
- Milk composition – pH
- Infant feeding behaviors
- Drug factors
Breastfeeding and Methadone

- The amount of methadone in the breast milk will vary with the fat content of the sample:
  - Foremilk (less fat) less methadone
  - Hindmilk (more fat) more methadone
  - Peak milk methadone levels 4 hours after oral
  - Average amount of methadone reported in breast milk 2.2% of the daily dose taken by the mother
  - Frequent small doses can prevent Neonatal Withdrawal Syndrome (NWS)

Ballard et. al J Perinatal Neonatal Nurs 2002
Breastfeeding and Methadone

- Small amount of methadone found in breast milk (not related to maternal methadone dose)
- Limited data suggest breastfeeding may decrease NWS symptoms
- Gradual weaning from breast is recommended to prevent NWS
- Women who are HIV positive and/or continuing to use illicit drugs should not breast feed
Breastfeeding and Buprenorphine

- Excreted in breast milk with milk:plasma ratio of 1
- Given the low bioavailability, infant exposure is approximately 1/5 to 1/10 of total buprenorphine
- Buprenorphine levels in breast milk may have little effect on NWS

Lactation Resources

- Internet
Methadone can increase serum prolactin. However prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Most infants receive an estimated dose of methadone ranging from 1 to 3% of the mother’s adjusted weight–adjusted methadone dosage.

The absolute dose in breast milk is less than the dosage used for treating NWS...
LactMed
Buprenorphine and Lactation

“Buprenorphine can increase serum prolactin. However prolactin level in a mother with established lactation may not affect her ability to breastfeed.”

“Because of the low levels of buprenorphine in breast milk, its poor oral bioavailability in infants, and the low drug concentrations found in the serum and urine of breastfed infants, its use is acceptable in nursing mothers”
Considerations for Effective OAT in Pregnancy

- Establish early collaboration/intervention between OB/GYN practitioner and OAT specialist and others
- Address concerns/barriers for outpatient treatment of NWS in the community
  - Breast feeding
  - Availability of medications
  - Risk for diversion of medication
  - Assessments of the infant (reliable)
  - Loss to followup
Opioid use in pregnancy is an ever increasing problem

Neonatal withdrawal secondary to intrauterine exposure is associated methadone or buprenorphine

Non-pharmacologic and pharmacologic interventions with methadone or buprenorphine are indicated

Long term neurodevelopmental effects need to be determined

Transition of care issues need to be addressed
Selected References


Selected References (cont’d)

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