FETAL EXPOSURE TO SUBOXONE/SUBUTEX

Goals and Objectives:

1. Discuss the management of maternal opioid dependence
2. Discuss the pharmacokinetics of buprenorphine
3. Review management plans for NAS following buprenorphine exposure

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Maternal Substance Abuse
MATERNAL SUBSTANCE ABUSE

Drug use is most prevalent in the reproductive age population. Women aged 15 to 44.
- Almost 90% have used alcohol.
- 44% have used marijuana.
- At least 14% have used cocaine.

Reduction in substance use may occur during pregnancy. Some women may not alter their drug use until pregnancy is diagnosed.

ACOG Tech Bull 195. 825-831. 1994

National Epidemiologic Survey on Alcohol and Related Conditions

Narcotic Exposure to Fetus

- No birth defects.
- Intrauterine withdrawal.
- Increased fetal activity.
- Depressed breathing movements.
- Preterm delivery.
- Preterm rupture of the membranes.
- Fetal growth restriction.
- Meconium stained amniotic fluid.
- Perinatal mortality.
- Neonatal abstinence syndrome.
- Sudden infant death.

SUBOXONE

Hexagonal orange tablet intended for sublingual administration.
- 2mg buprenorphine with 0.5mg naloxone.
- 8mg buprenorphine with 2mg naloxone.
SUBUTEX

Oval white tablet intended for sublingual administration
2mg buprenorphine and 8mg buprenorphine free base

Substance Use
Male to female ratio
• 1980s    5:1
• Recent surveys 3:1


History of Opioid Addiction

"The army disease."
Widespread prevalence documented in the United States following the U.S. Civil war of 1861–1865, when narcotics administered to injured soldiers (Hentoff, 1965).

History of Opioid Addiction
1860–1910
• The synthesis of heroin in 1874, "wonder drug."
• 1900s physicians, pharmacists, and patent medicine salesmen dispensed narcotics freely to middle-aged, middle-class women (Courtwright, 1992).
• By 1900, ~300,000 Americans were addicted to opiates (Courtwright, 1992).
History of Opioid Addiction
1910–1950
- Successive waves of immigration and urbanization contributed to a population of opioid abusers who were in their teens or early 20s.
- Unmarried, poor, primarily male, ethnic minorities who experimented with drugs for nonmedical purposes (Courtwright, 1992).

History of Opioid Addiction
1950–present
- IV heroin intensified in the United States after WWII.
- Epidemic of heroin in urban centers in 1950s and 1960s (Joseph, Stancliff, and Langrod, 2000).
- The 2003 NIDA - 3.7 million Americans had used heroin at some time in their lives and 314,000 in the past year.
- Heroin use in 2003 was stable at low levels (NIDA).

National Center on Addiction and Substance Abuse
- Girls and young women are more vulnerable to abuse and addiction, become dependent faster, suffer the consequences sooner than boys and young men.
- Women experience physiologic consequences related to alcohol misuse more rapidly than do men.
- Associated with domestic violence, rape, childhood sexual abuse, physical abuse, or neglect.

National Center on Addiction and Substance Abuse
- Women abusers are often judged more harshly for their behavior.
- Substance use extends to the unborn and live children.
- Unborn child is at risk for developmental delays, physical and neurologic deficits.
- Children are at higher risk for a behavioral, psychological, and emotional problems.
Fetal Exposure to Drugs

- Virtually any substance unbound to proteins passes freely from the maternal compartment, across the placenta, and into the fetal compartment, generally within minutes.
- Concentrations in the fetal circulation can be the same or higher than in the maternal serum.
- Effects on the fetus depends on the gestation and drug distribution.
- Passage of the drug or metabolite into the fetal CNS is unimpeded.

Past Alcohol Use & Substance Use During Pregnancy

Women who ever had alcohol
- 5 times more likely to currently use drugs
- 8 times more likely to currently use either drugs or alcohol or both

Women who drank in the month before pregnancy were about
- 11 times more likely to currently use drugs
- 41 times more likely to currently use either drugs or alcohol or both

2006 National Survey on Drug Use and Health Reports

Females age 12 years or older in the united states
- ~ 41% used an illicit drug(s) at some point in their lives
- 6% were current users of illicit drugs
- 23% used tobacco
- 45% used alcohol
- 3% used alcohol heavily
- 15% were binge drinkers

Alcohol

- 1950s male/female ratio of initiation in the 10- to 14-year-old age group was 4:1, and by the early 1990s it was 1:1
- Women experience significantly shorter time intervals between the initiation of alcohol use and alcohol-related problems
- Women have lower percentage of total body water, lower levels of alcohol dehydrogenase in the gastric mucosa, and slower rates of alcohol metabolism
**Alcohol**

- Women consume alcohol in response to stress and negative emotions.
- Men seem more likely to consume alcohol to enhance positive emotions or to conform to a group.
- Women with alcohol-use disorders are significantly more likely to have psychiatric disorders.
- Women are less likely than men to seek treatment.

**Alcohol Use in Pregnancy**

- Microcephaly
- Growth deficiency
- CNS dysfunction
- Mental retardation
- Behavioral abnormalities
- Short palpebral fissures, hypoplastic philtrum, flattened maxilla
- Abortion
- Still birth

**Effect of Fetal Marijuana Exposure**

- "Grass"; "Pot"; "Reefer"; "Joint"; "Hashish"; "Cannabis"; "Weed"
- About 1 in 3 Americans has used marijuana at least once
- ~10% of the population uses it on a regular basis
- No anomalies
- Decrease in birth weight
- Subtle behavioral alterations
- VSD

**Amphetamines/Cocaine**

- Abortion
- Excess activity in utero
- Congenital anomalies (heart?, Biliary atresia?)
- Depression of interactive behavior
- Urinary tract defects
- Symmetric growth restriction
- Placental abruption
- Cerebral infarction
- Brain lesions
- Cranial defects
- Fetal death
- Neonatal necrotizing enterocolitis
- Shortened labor
Smoking & Substance Use

Women who had ever smoked
4 times more likely to currently use drugs
6 times more likely to currently use either drugs or alcohol
Women who smoked in the month before pregnancy
11 times more likely to currently use drugs
9 times more likely to currently use either drugs or alcohol or both


High Risk for Substance Abuse

Moderate or severe depression
Women who lived alone or with small children
Women who lived in urban areas or suburbs
Women who lived with someone who used drugs or alcohol


New Epidemic

Prescription Drug Abuse

- Many young people are prescribed Ritalin and Adderall for ADD/ADHD.
- High percentage of these young people sell or share their “medications” with their peers.
- Advertisements for sleeping aids, tranquilizers and other mood-altering drugs on TV suggests that life is better with chemical support.
- Millions of parents are given these prescription drugs by their physicians.
- Teens are getting prescription drugs for free (home medicine cabinets).
- Physicians prescribing opiate painkillers to young people
Illegal use of Prescription Drugs

- The illegal use of OxyContin, as well as other prescription drugs, has increased recently.
- 1999 NHSDA showed ~ 9% of the U.S. Population (20 million) had used pain relievers illegally in their lifetime.
- ~ 1.6 million Americans used prescription-type pain relievers non-medically for the first time in 1998.
- From 1990 to 1998 for 12-17 year old, the incidence rate increased from 6.3 to 32.4 per 1,000.
- For 18-25, there was increase from 7.7 to 20.3 per 1,000.

2004 National Survey on Drug Use and Health

- Lifetime non-medical use of prescription pain relievers among young adults (aged 18–25):
  - 22.1% in 2002
  - 23.7% in 2003
  - 24.3% in 2004
- ~ 1 in 10 reported the misuse of a sedative at some time in their life.
Prescription Opioids

- 1992 to 2003: 141% increase in prescription opioid abuse
- Abuse more often in women than men
- 2002 to 2004 national survey on drug use and health (NSDUH) found that women aged 12 to 17 years had higher rates than men for opioid use

Prescription opioids

- Among college students, men were significantly more likely than women to use prescription opioids
  - For experimentation: 35.3% vs 18.4%
  - To get high: 39.4% vs 24.4%
  (McCabe and colleagues)
- Women with chronic pain were significantly more likely than men to hoard unused medications and to use additional drugs to enhance the effectiveness of prescription opioids
OxyContin

- Aggressively marketed by Purdue.
- Introduced in 1995
- By 2003 nearly half of all OxyContin prescribers were primary care physicians.
- The active ingredient in OxyContin is twice as potent as morphine.
- Sales increased rapidly following its introduction to the marketplace in 1996.
- By 2001, sales had exceeded $1 billion annually.

OxyContin

- It is a sustained-release preparation typically used for moderate-to-severe pain control
- Among pain relievers, the use of OxyContin has been increasing since it first became available in 1995
- In 2004, there were 615,000 new users of OxyContin with an average age of first use 24.5 years
- Usage of OxyContin increased between 2002 and 2004 for 8th, 10th, and 12th graders

OxyContin

- OxyContin, also referred to as "oxy," "O.C.," and "killer" on the street
- Semi-synthetic opioid analgesic
- Active ingredient is oxycodone
- OxyContin contains between 10 and 160 milligrams of oxycodone in a timed-release tablet
- Oxycodone is also found in Percodan and Tylox
- Provides 12 hours of relief from chronic pain

Why Is OxyContin Abuse Much Greater?

- By crushing the tablet and either ingesting or snorting it, or by injecting diluted OxyContin, abusers feel the powerful effects of the opioid in a short time, rather than over a 12-hour span
- 40 mg pill costs ~$4 by prescription, sells for $20 to $40 on the street
- OxyContin can be comparatively inexpensive if it is legitimately prescribed and if its cost is covered by insurance
Vicodin (hydrocodone)

- Synthetic narcotic also typically used for pain control.
- In 2005, the annual prevalence for usage of Vicodin in 8th, 10th, and 12th graders was 2.6%, 5.9%, and 9.5%.

Risk Factors for Opioid Use

- Female gender
- Black race
- Lower socioeconomic status
- Favorable attitudes toward illicit drugs
- Detached parents
- Friends who use illicit drugs

Medications for Opioid Dependence

- Methadone
- Naltrexone
- LAAM (L-alpha-acetyl-methadol)
- Buprenorphine

L-alpha-acetyl-methadol (LAAM)

- Potent opioid with a longer duration of action than methadone
- Can suppress opioid withdrawal for up to 72 hours
- Comparable to MMT
- Reports of QT prolongation and episodes of Torsades de point
- Removed from the European markets and limited use in USA
**Naltrexone**

- An opioid receptor antagonist used primarily in the management of alcohol/opioid dependence
- It reversibly blocks or attenuates the effects of opioids
- Used in rapid detoxification, preferably under anesthesia
- The effect is similar to naloxone but it is prolonged
- No effect on craving
- Questionable efficacy in long-term opioid dependence management

**Role of Drug Intervention in Pregnancy**

Even minimal drug interventions (such as MMT) and counseling, combined can lead to better pregnancy and infant outcomes.


**Current Medications for Opioid Dependence**

**Methadone** can be dispensed in a very limited number of clinics that specialize in addiction treatment.

**Subutex** and **Suboxone** are available for the treatment of opiate dependence that can be dispensed in an office setting.

**Methadone**

- Well-tested and safe
- Has been used to treat opioid addiction in the United States for > 40 years
- Blocks the craving for opioids
- Suppresses the symptoms of opioid withdrawal for 24 to 36 hours
- Blocks the effects of administered heroin
- Does not cause euphoria, intoxication, or sedation
Advantages of Methadone

- Lower cost
- More effective in patients with higher tolerances
- Treatment retention rates are higher

Methadone safety for Pregnant Women and their Infants

Reduces adverse pregnancy outcomes
Reduces adverse birth outcomes
Infant withdrawal is treatable
Shows no long-term adverse neurobehavioral effect of fetal exposure

Effect of MMT

- Reduction in criminal activity
- Reduction in needle sharing
- Reduction in HIV infection rates and transmission
- Cost-effective
- Reduction in commercial sex work
- Reduction in the number of reports of multiple sex partners
- Improvements in social health and productivity
- Improvements in health conditions
- Retention in addiction treatment
- Reduction in suicide
- Reduction in lethal overdose
Effect of Methadone on Drug use and Crime

International NIDA Program

Effect of Functional Status with MMT

HIV Seroconversion Rate MMT Program

Effect of Methadone on weekly heroin use Hubbard et al., 1989
MMT Effect on Drug Use

- Hepatitis types A, B, C, STDs, BE, sepsis, and cellulitis, seen commonly among active injection drug users, is less likely with MMT.
- Obstetrical complications such as spontaneous abortion, placental insufficiency, and other conditions occur at a lower rate.
- Better overall health and nutritional status during methadone.
- Clinics can provide onsite prenatal services or link patients to these services in nearby clinics.

Can we reduce methadone dose or detoxify women from methadone during pregnancy to protect the fetus?

- No!!!
- Withdrawal leads to opioid abstinence syndrome, which is harmful to the pregnancy and often leads to relapse to illicit drug use.
- Dosage change in pregnancy must be carefully evaluated.
- Some need an increase in dosage or split (e.g., Twice daily) dosing.
- Woman steadily maintained on methadone have a healthy pregnancy.
- No withdrawal is noted when methadone is individually determined and properly administered.
- Long-term MMT of 80 to 120 mg per day is not toxic or dangerous up to 14 years in adults.

MMT In Pregnancy

- Obstetrical complications such as spontaneous abortion, placental insufficiency, and other conditions occur at a lower rate.
- Better overall health and nutritional status during methadone.
- Clinics can provide onsite prenatal services or link patients to these services in nearby clinics.

Fetal Effects of MMT

- Methadone crosses the placenta.
- NAS depends on other drugs during pregnancy, anesthesia during delivery, the maturational and nutritional status of the infant, and other aspects of maternal health that affect the fetal environment.
- Length and severity of the withdrawal is variable.
- Pharmacotherapy for neonatal methadone abstinence syndrome is effective.
- MMT protects fetus from erratic maternal opioid levels.
Cost savings with MMT

- Savings of medical costs, law enforcement costs, judicial system costs, corrections costs, non drug crime costs, drug traffic control, drug abuse prevention costs, absenteeism costs, unemployment costs, and drug-related deaths.
- Overall cost-effective and beneficial to society.
- A single dollar spend on MMT saves 3 dollars in future costs.

*Rufener et al., 1977*

Buprenorphine

- Approved for opioid dependence in Australia, Belgium, Canada, Croatia, Germany, Iran, England, France, UK, USA.
- Partial agonist at the opioid receptor, as opposed to a full agonist such as methadone or heroin.
- Unique pharmacologic profile leading to a lower likelihood of overdose or respiratory depression.
- Like methadone it has the ability to suppress opioid craving and withdrawal.
- It blocks the effects of self administered opioids.
- Retains patients in treatment.
- Decreases illicit opioid use.
**Buprenorphine**
- Metabolized in liver
- Mostly excreted in stools
- <30% in urine
- Elimination 1/2 life = 37 hrs
- Norbuprenorphine is the active metabolite
- Analgesic effect X 25-40 of morphine

**Common side effects**
- Constipation
- Urine retention
- Sedation
- Mild resp. depression, not reversed by naloxone

**Potential for Abuse**
- Can overdose if given IV with benzodiazepines
- No abuse with SL use
- No abuse with suboxone IV, naloxone reverses opioid effect

**Buprenorphine, Pregnancy and Nursing**
- Category C (methadone is category B)
- Can be used in pregnancy
- It is excreted in breast milk
- GI uptake in infant is low
- Nursing is continued
The Drug Addiction Treatment Act of 2000

- Allows qualified physicians to dispense or prescribe specifically approved schedule III, IV, and V narcotic medications for the treatment of opioid addiction in treatment settings other than the traditional Methadone clinic.
- Waives the special registration requirements for MDs.
- 30 patient limit for first year and the 100 patient limit thereafter.

Buprenorphine Abuse

- As a partial agonist, buprenorphine has less potential for abuse.
- IV buprenorphine can lead to a painful and uncomfortable precipitated withdrawal.
- Buprenorphine with naloxone, in a 4 to 1 ratio, has demonstrated decreased abuse potential and withdrawal (Mendelson, Jones, Welm, et al., 1999).
- With sublingual suboxone, naloxone is poorly absorbed, and the patient receives a buprenorphine effect.
- If dissolved and injected, the naloxone will antagonize the buprenorphine, blocks opioid effects and precipitates immediate withdrawal.

Rules of Engagement for Buprenorphine

Pregnancy is not an indication for emergent treatment in the absence of other medical/obstetric complications.
Admissions are scheduled and if appoints are missed, they are rescheduled.
Non-compliance may result in loss of opiate agonist therapy (although criteria are much less stringent that the non-pregnant population).

Buprenorphine

- Buprenorphine occupies opioid receptors with great affinity.
- Blocks opioid agonists from exerting their effects.
- It dissociates from opioid receptors at a slow rate.
- Daily or less frequent dosing of buprenorphine, 3/week in some studies.
Indications for Buprenorphine Use

- Subjects are interested in treatment for opioid addiction
- Have no contraindications to buprenorphine treatment
- Can be expected to be reasonably compliant with such treatment
- Understand the benefits and risks of buprenorphine treatment
- Agree to treatment after a review of treatment options

Patients Less Likely to Be Appropriate Candidates for Buprenorphine

- Comorbid dependence on high doses of benzodiazepines or other CNS depressants (including alcohol)
- Significant untreated psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Poor response to previous treatment attempts with buprenorphine
- Significant medical complications

Buprenorphine vs. Methadone

Advantages of buprenorphine

- Higher doses have lower risk of toxicity
- Potentially effective at less than recommended daily dosage
- Withdrawal symptoms are less severe after discontinuation
- Less abuse potential
- More accessible for office-based treatment programs

Buprenorphine

- Even high doses of buprenorphine, as much as 100 times the dose for analgesia, do not produce dangerous respiratory effects.
- Respiratory depression caused by buprenorphine is not of clinical concern which makes it an extremely attractive treatment alternative.
Side Effects of Buprenorphine
- Similar to those of other opioids
- Include nausea, vomiting, and constipation
- Can precipitate the opioid withdrawal syndrome

Withdrawal From Buprenorphine
- Piloerection
- Diarrhea
- Yawning
- Mild fever
- Insomnia
- Craving
- Distress/irritability
- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lactation
- Rhinorrhea
- Pupillary dilation
- Sweating

Phases of Buprenorphine Maintenance Therapy
- Induction
- Stabilization
- Maintenance

Switching from Methadone
- A longer time interval between methadone and subsequent buprenorphine dosing is recommended depending on the dose of methadone
- With 20 to 40 mg of daily methadone, the transition to buprenorphine is less difficult and can generally be initiated 24 hours after the last dose of methadone
- For higher doses of methadone, delay initiation of buprenorphine >24 hours after the last dose of methadone or rapidly lower the dose of methadone and offer supportive therapy with ancillary medications prior to buprenorphine induction
Methadone Maintenance Programs

- Stringent entry criteria
- Long waiting list
- Usually in urban areas
- Only 14% of opioid users are in clinics

Available forms of Buprenorphine

In USA: Suboxone & Sebutex for SL Use
- IV buprenex is not approved by FDA
- Europe: Transdermal patches, IV
  - IM for use for dogs (Vetergesic in UK)
- In India: Slow release oral, IV, spinal anesthesia
- Implantable (Probuphine)-polymer matrix sustained release technology for addiction treatment
- FDA approved BioErodible Mucoadhesive technology is being developed for chronic and post-op pain

NAS in Neonate exposed to Buprenorphine

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Total admissions: 4119
**NICU Admissions for NAS 2000-2009**

- Average LOS with methadone: 26 days
- Range of DOS with methadone: 5-58
- Average LOS with other drugs: 20.6 days
- Range LOS with other drugs: 1-74
- Cost of care/admission with methadone: $72,800
- Cost of care/admission with other drugs: $57,680

*Assumption: Cost of care in NICU per day = $2,800*

**NICU Admissions for NAS 2000-2009**

- Sebutex/suboxone exposure first noted in 2007
- 22 NICU admissions were related to subutex & suboxone in 2 years from 2007-2009
- Subutex/suboxone exposure ~ 2.5% of all NICU admissions
- Average LOS with subutex/suboxone: 19 days
  (range 3 days to 54 days)

**NAS following buprenorphine exposure**

- NAS with buprenorphine is similar to methadone.
- 6 mg a day of subutex or suboxone can present with significant withdrawal in infant.
- The duration of hospital stay for a newborn infant with a need for drug therapy could be from 5 days to 60 days based on the severity of NAS.
- Infants delivered under 30 weeks gestation generally have mild or no clear evidence of NAS.
- Severity of RDS is mild in preterm infants.
- Associated use of sedatives can potentiate NAS.

**Drug Therapy for NAS following buprenorphine exposure**

- It is similar to methadone related NAS
- Buprenorphine is not approved or recommended for neonatal NAS
- Morphine or methadone is recommended for persistent NAS score of equal or more than 12
- Phenobarb has no role in the management of NAS
- FDA monitored studies are in progress to evaluate use of buprenorphine for NAS.
Medical Management of NAS following buprenorphine exposure

Management of NAS is in 3 stages:
- **Initiation:** 12-48 hours
- **Stabilization:** this phase generally takes 3-7 days
- **Weaning:** This phase is the longest considering that dose is decreased 10 to 15% every 3rd day. Occasional infant may be weaned more rapidly

Not every infant with NAS requires medical management

Management of NAS following buprenorphine exposure

- Duration of observation for NAS
- Admission to NBN or NICU
- Cost of care
- Morphine vs methadone
- Follow-up care

Summary

- There has been a steady rise in maternal drug use in last 2 decades
- Prescription drug use has taken epidemic proportions
- Subutex and suboxone are currently dispensed for maternal opioids dependence
- Observation of infant with fetal exposure to buprenorphine is recommended
- Drug therapy may be needed with buprenorphine exposure in utero

Thank You!