MethaDONe, MethaDON’T and the Care of the Pregnant Substance Abuser

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Goals

- Understand the scope of substance abuse in the US as it relates to gender and pregnancy
- Appreciate the importance of screening for substance abuse in pregnancy
- Understand the pharmacology of methadone and the evolution of its current use
Goals

- Accept the delicate balance of risk and benefit associated with methadone exposure in pregnancy
- Expose the controversy regarding maternal detoxification in pregnancy
- Explore alternatives to methadone for opiate substitution
Substance Abuse in the US

An estimated 20.4 million Americans aged 12 and older are current illicit drug users.
Substance Abuse in the US

810,000-1 million chronic opioid (heroin) users
- At least 6.4 million abusers of prescription narcotics
- 12-17 y.o.: 12%, 18-25 y.o. 22% report prescription opioid abuse
- 1994-2001 ED visits: 352% increase in oxycodone visits, 131% increase in hydrocodone visits
- Currently only 240,000± patients receiving methadone maintenance
- In 4 states, and in some counties in other states, public policy prohibits establishment of Opiate Treatment Programs
- Detoxification has been shown to be of limited long-term effectiveness
- Access to treatment restricted
GROVE CITY, Ohio — For five hours, Dana Smith huddled stunned and bewildered in her suburban living room while the body of her son Arthur Eisel IV, 31, lay slumped in an upstairs bathroom, next to a hypodermic needle.
Opiate Abuse in Ohio

Heroin Abuse Growing in Ohio

In recent years, deaths from heroin overdoses have spread beyond the state's urban centers as heroin abuse has expanded into rural and suburban areas. Though most federal drug cases still involve cocaine or marijuana, the share of drug prosecutions that are heroin-related in the Southern District of Ohio, which includes Columbus, Dayton and Cincinnati, has risen to 15 percent from 4 percent a decade ago.

Sources: Ohio Department of Health, U.S. Attorney's Office, Southern District of Ohio
DRUG OVERDOSE DEATHS, OHIO¹ VS. US², 1999-2008 (2010 FOR OH)

Source: 1. ODH Office of Vital Statistics 2. CDC WONDER,
Unintentional Drug/Medication Poisoning Death Rates per 100,000 by County, 2006-2010

Ohio – 12.2 per 100,000

Death rates per 100,000
- <6.0
- 6.0 – 8.9
- 9.0 – 12.2
- 12.3 – 16.9
- 17.0 – 26.0

Source: ODH Office of Vital Statistics
TEENS AND PRESCRIPTION DRUG ABUSE

According to surveys:

• **In 2011, more than 1 in 5 (21%)** Ohio high school students reported using a prescription drug without a doctor’s prescription one or more times during their life. **Of these teens, nearly half (49%) used narcotic pain relievers, 8 percent used multiple drugs and another 19 percent were unsure what they took.**

• Every day, **2,700 teens** abuse a prescription drug for the first time.

• **8 out of 10 teens** who misuse prescription drugs get the drugs from friends or relatives

Sources: 1. ODH, Ohio Youth Risk Behavior Survey, 2011
2. SAMHSA’s National Survey on Drug Use and Health
CHANGES IN CLINICAL PAIN MANAGEMENT PRESCRIBING PRACTICES IN LATE 1990’S

In 1998 the Federation of State Medical Boards of the United States, Inc. provided its policy document

- Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

Recognition of Pain as the “5th Vital Sign”

Pain relief laws were pushed down to states to address liability concerns among prescribers.

- Ohio Revised Code 4731.21 Drug Treatment of Intractable Pain, 1997

Contributed to increased availability of potent pain medications in the community setting that had been previously restricted to hospital use for pain (e.g., end-stage cancer) patients.

*Intractable Pain Relief Act
PAINKILLER SALES SOAR AROUND US, FUEL ADDICTION

• Nationwide, pharmacies received and ultimately dispensed the equivalent of 69 tons of pure oxycodone and 42 tons of pure hydrocodone in 2010.

• That's enough to give 40 5-mg Percocets and 24 5-mg Vicodins to every person in the United States.

Source: Associated Press, April 5, 2012
## Opioid Distribution in Ohio, 2010

<table>
<thead>
<tr>
<th>Opioids</th>
<th>2010 doses in Ohio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone (e.g., Vicodan)</td>
<td>303,268,137</td>
</tr>
<tr>
<td>Oxycodone (e.g., OxyContin, Percocet)</td>
<td>282,936,529</td>
</tr>
<tr>
<td>Methadone</td>
<td>30,908,359</td>
</tr>
<tr>
<td>Morphine (e.g., Opana)</td>
<td>25,902,895</td>
</tr>
<tr>
<td>Codeine</td>
<td>24,838,334</td>
</tr>
<tr>
<td>Hydromorphone (e.g., Dilaudid)</td>
<td>9,739,798</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>9,285,455</td>
</tr>
<tr>
<td>Fentanyl base</td>
<td>4,457,848</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>742,850</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>692,080,205</strong></td>
</tr>
</tbody>
</table>

In 2010, 692 million opioid doses were distributed to retail pharmacies in Ohio. That’s enough to provide 60 opioid doses to every single Ohioan.

- Or the equivalent of:
  - 1.8 million doses per day
  - 79,000 doses per hour
  - 1,316 doses per min.
  - 22 doses per second

Source: DEA, ARCOS Reports, Retail Drug Summary Reports by State, Cumulative Distribution Reports (Report 4) Ohio, 2010 4. US Census Bureau, Ohio population estimates 2010
NATIONAL DATA: PUBLIC HEALTH IMPACT OF OPIOID OVERDOSE

In 2008, there were 14,800 prescription painkiller deaths.™

For every 1 death there are...

10 treatment admissions for abuse™
32 emergency dept visits for misuse or abuse™
130 people who abuse or are dependent™
825 nonmedical users™

Sources: ¹SAMHSA Treatment Episode Data Set (TEDS); ²Drug Abuse Warning Network (DAWN); ³National Survey of Drug Use in Households (NSDUH)
DIVERSION: A LUCRATIVE BUSINESS

PHARMACY PRICE
$.09 to $.13 per mg
$7-8 per 80-mg tablet
$750 for 100 80-mg tablets

STREET VALUE
$1 per mg
$80 per 80-mg tablet
$6,000-8,000 for 100 80-mg tablets

Source: DrugStory Factsheet: Abuse of Prescription Painkillers
Pill Mills and Unscrupulous Prescribers

9 pain management clinics ("pill mills") in Scioto County: a county of 76,000 people.

Scioto County dispensed roughly 35 million oxycodone and hydrocodone pills in 2010: equals 46 pills for every Scioto County resident.
## Estimated average annual costs of unintentional drug overdose in Ohio

<table>
<thead>
<tr>
<th>Type of Costs</th>
<th>Fatal Costs(^2)</th>
<th>Non-fatal, hospital admitted costs(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>$4.9 million</td>
<td>$19.1 million</td>
</tr>
<tr>
<td>Work loss</td>
<td>$1.2 billion</td>
<td>$5.2 million</td>
</tr>
<tr>
<td>Quality-of-Life loss</td>
<td>$2.2 billion</td>
<td>$7.6 million</td>
</tr>
<tr>
<td>Total</td>
<td>$3.5 Billion</td>
<td>$31.9 Million</td>
</tr>
</tbody>
</table>

\(^1\)Source: Children's Safety Network Economics & Data Analysis Resource Center, at Pacific Institute for Research and Evaluation, 2005; \(^2\)Year 2004 Dollars, Based on 2004-2007 average Ohio incidence; \(^3\)Year 2005 Dollars, Based on Year 2003 Ohio incidence
Substance Abuse in the US

- 4.5 million women in this country abuse alcohol
- 3.5 million women abuse prescription drugs
- 3 million women regularly use illicit drugs
Substance Abuse in the US

- Women develop more severe sequelae of addiction than men

- Transition of illicit drug use to abuse is more rapid
Substance Abuse in the US

- Substance use during pregnancy is estimated at 4-5%, ranging 0.4%-27%
Substance Abuse in the US

Pregnant
- Cocaine: 27%
- Alcohol: 24%
- Opiates: 19%
- Marijuana: 14%
- Stimulants: 12%
- Other: 4%

Nonpregnant
- Cocaine: 20%
- Alcohol: 38%
- Opiates: 19%
- Marijuana: 11%
- Stimulants: 8%
- Other: 4%
Substance Abuse in the US

- **Opiates**
  - Heroin: aka skag, junk, H or smack, black tar
  - Heroin use is estimated at 1/1000, stable
  - Oxycontin (O.C.s, ox, oxy, Hillbilly Heroin) abuse has more than quadrupled since 1999
Substance Abuse in the US

- Opiates are exceedingly addictive
- Heroin use strongly influenced by a male partner
- Women initiate use earlier in life than men
- Women more likely to inhale heroin than inject
- Women develop heroin dependence more rapidly than men
Substance Abuse in the US

- Opiates in pregnancy: at least 7000 births per year
  - Preterm birth
  - Low birth weight
  - Perinatal mortality
  - Neonatal Abstinence Syndrome
  - Long term neurobehavioral abnormalities
Screening for Substance Abuse

- We have an obligation to screen for illicit drug use in pregnancy
  - Only 20% of us do so

- Responsibility to mother and neonate
Screening for Substance Abuse

- Self report is not often used in the setting of drug abuse
  - Higher levels of physician discomfort discussing
  - Self report tools are less plentiful
  - CAGE-AID, DAST, ASI

- Urine toxicology is the standard for screening
Screening for Substance Abuse

- Make your questions assumptive
  - “Which street drugs have you used more than 5 times in your life?”
- Look for suggestive behaviors
  - Medical Conditions (STDs, Heart disease)
  - Psychiatric Disease (Depression, Bipolar)
  - Poor dentition, poor nutrition
  - PTL, PPROM, Abruption
  - Chronic Unemployment, Poor PNC, Incarceration or Prostitution
Methadone

- Developed in Germany as an alternative to morphine during WWII
- Synthetic opioid
- Mu opioid receptor agonist and a weak NMDA receptor antagonist
- Metabolized by the cytochrome P450 system
Methadone

- Methadone has many desirable qualities
  - Highly bioavailable
  - Long half life
  - Low cost
  - Convenient dosing
  - Slow onset to withdrawal syndrome
Methadone

- The primary uses are now for chronic pain and opioid addiction
Methadone

- 1919: Supreme Court decision establishes that addiction alone did not justify physicians treating addicts with opioids.
Methadone

- 1965: Vincent Dole, MD, and Marie Nyswander, MD published the first small clinical trial of methadone for treatment of heroin addiction
Methadone

- By 1970: Thousands were being treated with methadone maintenance: “experimentally”

- 1971-1974: Returning Vietnam vets increasingly found to be heroin addicted: Prompting the establishment of the Special Action office of Drug Abuse Prevention. A nationwide network of methadone treatment clinics established
Methadone

- 1980s: The emergence of AIDS increased the urgency to treat individuals with opiate addictions

- It was documented that the rates of HIV were lower in methadone maintained individuals than IV heroin abusers
Methadone and Addiction

- Methadone has been used for more than 40 years in the treatment of addiction
- Important benefits include deterrent from high risk behaviors, incarceration, spread of STDs
- Addicts remain opiate dependent, but functional
Methadone and Addiction

Figure 1. Outpatient methadone treatment (OMT): pretreatment and posttreatment statistics

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine use (weekly)*</td>
<td>42</td>
</tr>
<tr>
<td>Heroin use (weekly)*</td>
<td>89</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>15</td>
</tr>
<tr>
<td>Illegal activity*</td>
<td>29</td>
</tr>
<tr>
<td>No full-time employment</td>
<td>85</td>
</tr>
</tbody>
</table>

% of DATOS Sample (N=727)

*p<0.001

Similar benefits have been identified in the pregnant woman maintained on methadone as in the non-pregnant population
Methadone and Mothers

- Methadone Maintenance associated with better prenatal care
  - Earlier, more compliant
- Improved nutrition and weight gain
- Better preparation for parenting
- Less children in the foster care system
- Improved enrollment in substance abuse treatment and recovery
Methadone and Mothers

- Methadone can be difficult to dose
- Many symptoms of withdrawal are similar to pregnancy associated symptoms
- Decreased absorption
- Rapid Elimination
- Higher Clearance
- As pregnancy progresses they may need more drug
Methadone and Mothers

- Analgesic Needs
  - Intrapartum pain management not different from standard populations
  - Post vaginal delivery, reported pain scores higher in methadone maintained individuals but use of narcotics similar
  - Postcesarean, especially immediately, narcotic requirements 70% higher in methadone maintained women
Methadone and Mothers

General Approach to Analgesia

- Continue maintenance dosing
- Treat pain aggressively immediately post partum
- By the time of discharge, most can be maintained on standard narcotic doses and NSAIDs
Methadone and Babies

- Crosses the placenta readily
  - Can reach 1/4 the concentration of maternal serum in cord blood

- Crosses the placenta in varying degrees throughout gestation
  - Ex vivo studies indicate the possibility of increased enzymatic efficiency and protein transfer in third trimester...increased methadone in the fetal compartment
Methadone and Babies

- Fetal weight better than heroin exposed fetuses
- Still fetal weights are less than those who are not drug exposed
Fetal response to maternal methadone administration

Lauren M. Jansson, MD, a, * Janet DiPietro, PhD, b Andrea Elko, PA-C c

Department of Pediatrics, Johns Hopkins University School of Medicine, a Department of Population and Family Health Sciences, John Hopkins Bloomberg School of Public Health, b and Department of Obstetrics and Gynecology, Johns Hopkins Bayview Medical Center, Baltimore, MD c

- At peak methadone (2-4 hours post administration), FHR slower, less variable, fewer accelerations, less motor activity
- Those with higher doses showed greater changes in variability
Methadone and Babies
Methadone and Babies

The effect of maternal methadone use on the fetal heart pattern: a computerised CTG analysis

R Navaneethakrishnan, S Tutty, C Sinha, SW Lindow
Department of Obstetrics and Gynaecology, Hull and East Yorkshire Women and Children’s Hospital, Hull Royal Infirmary, Hull, UK
Correspondence: Dr R Navaneethakrishnan, Department of Obstetrics and Gynaecology, Hull and East Yorkshire Women and Children’s Hospital, Hull Royal Infirmary, Hull HU3 2JZ, UK. Email rajikrishnan@doctors.org.uk

Accepted 2 June 2006.

- When compared to gestational age and parity matched women: methadone exposed fetuses showed a significant reduction in fetal heart rate baseline and number of accelerations.
Intrapartum FHR tracings identified lower baseline, less variability, and lower proportions of accelerations during the first stage of labor.
Methadone and Babies

- During the second stage, a higher proportion (44.2% vs 22.9%) of methadone exposed infants had late or severe variable decelerations.

- No significant difference between assisted delivery, cesarean delivery or Apgars noted.
Methadone and Babies

- Neonatal effects
  - Neonatal arrhythmias, prolonged QT
Methadone and Neonatal Abstinence Syndrome (NAS)

- NAS is seen with a variety of substances
  - Opiates
  - Alcohol
  - Barbiturates
  - Amphetamines
  - Cocaine
  - SSRIs
NAS

- 60-90% of infants born to methadone maintained mothers will experience NAS
- Withdrawal is usually more severe than that associated with heroin
- Usual onset is 2-3 days of life
- Treatment includes: methadone, phenobarbital, paregoric, morphine
NAS

Characterized by:

- CNS irritability
- Respiratory Distress
- GI dysfunction
- Autonomic Instability
NAS

- Classified by the Finnegan Scoring System or the Lipsitz Scoring System
<table>
<thead>
<tr>
<th>Central Nervous System Disturbances</th>
<th>Signs and Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excessive high-pitched (or other) cry &lt; 5 mins</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Continuous high-pitched (or other) cry &gt; 5 mins</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 1 hour after feeding</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 2 hours after feeding</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sleeps &lt; 3 hours after feeding</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hyperactive Moro reflex</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Markedly hyperactive Moro reflex</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mild tremors when disturbed</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe tremors when disturbed</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild tremors when undisturbed</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Moderate-severe tremors when undisturbed</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Increased muscle tone</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Excoriation (chin, knees, elbow, toes, nose)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Myoclonic jerks (twitching/jerking of limbs)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Generalised convulsions</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Hyperthermia 37.2-38.3°C</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Hyperthermia &gt; 38.4°C</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Frequent yawning (&gt; 3-4 times/scoring interval)</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Sneezing (&gt; 3-4 times/scoring interval)</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Nasal flaring</td>
<td>2</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Respiratory rate &gt; 60/min</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic/Vasomotor/Respiratory Disturbances</td>
<td>Respiratory rate &gt; 60/min with retractions</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Excessive sucking</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Poor feeding (infrequent/uncoordinated suck)</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Regurgitation (≥ 2 times during/post feeding)</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Projectile vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Loose stools (curds/seedy appearance)</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal Disturbances</td>
<td>Watery stools (water ring on nappy around stool)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Total Score**

**Date/Time**

**Initials of Scorer**
NAS

- A Finnegan score of greater than 8, twice in 24 hours or a score of >12 on any occasion warrants treatment.

- Length of treatment depends upon neonatal response, goal of Finnegan score less than 8 during taper.
NAS

- Treatment is ceased when neonate is free of signs for 24-48 hours

- Length of treatment is widely variable
  - Days to weeks
  - Average at OSU is 26 days, ranging up to 3 months
NAS

- The effect of maternal methadone dose upon NAS is an area of controversy.
Maternal methadone dose and neonatal withdrawal

Vincenzo Berghella, MD, Pearl J. Lim, MD, Mary K. Hill, RN, BSN, Jennifer Cherpes, BA, Jennifer Chennat, BA, and Karol Kaltenbach, PhD

Philadelphia, Pa

- AJOG 2003
- Retrospective chart review of 100 mother/infant pairs maintained on methadone
- Divided groups on <80mg and >80 mg
- Found similar highest Neonatal abstinence score, need for treatment, and length of treatment
- Higher incidence of illicit use in those <80 mg
Study of 25 methadone exposed mother infant pairs
Assessed the correlation of maternal dose, cord blood methadone concentration, and neonatal serum methadone concentration at 2 days of life
No correlation between maternal dose and need for treatment
Low cord blood concentration and undetectable day two levels were predictive of need for NAS treatment
High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes

John J. McCarthy, MD, a,* Martin H. Leamon, MD, b Michael S. Parr, MD, c Barbara Anania, PsyD a

Bi-Valley Medical Clinic, Sacramento, CA, a Department of Psychiatry and Behavioral Science, University of California, Davis, CA, b and private practice, Sacramento, CA c

Received for publication September 22, 2004; revised March 11, 2005; accepted March 30, 2005

• AJOG 2005
  • Retrospective chart review of 81 mother/infant pairs
  • Cohort divided into <100 mg and >100 mg
  • No differences in rate of medication treatment for NAS or length of stay
  • High Dose group had less illicit substance abuse at delivery
Relationship Between Maternal Methadone Dosage and Neonatal Withdrawal

Jodi S. Dashe, MD, Jeanne S. Sheffield, MD, Debora A. Olscher, RNC, NP, Sally J. Todd, RN, CPNP, Gregory L. Jackson, MD, and George D. Wendel, Jr, MD

- Obstetrics and Gynecology, 2002

- Retrospective review of 70 mother infant pairs
- Median dose was 20 mg
- Analyzed <20 mg, 20-39 mg, and >40 mg
- NAS necessary for treatment identified in 12%, 44% and 90% respectively
- Also correlated with duration of stay and peak neonatal abstinence score
NAS

- Lim, et al, AJOG Jan 2009
  - Retrospective chart review of 68 mother/infant pairs at The Ohio State University
  - Mean methadone dose 97 mg (15-240 mg)
  - 77% required treatment for NAS
  - Every increase of 5.5 mg of methadone correlated to an additional day of NAS treatment
NAS

- Higher methadone doses may decrease illicit drug use and high risk behaviors, and may not impact NAS
  - Is there a role for pharmacogenomics?

- Lower doses intuitively seem to be a goal
NAS

Is it reasonable to consider LOWERING doses in advancing gestation given:

- Increase maternal clearance
- Rapid elimination
- Decreased absorption
NAS

- Do we have any other way of intervening and limiting NAS?

- What is the role of indicated preterm delivery?
NAS

  - Retrospective cohort of 53 preterm and 66 term mother infant pairs
  - Preterm infants required lower doses of medication for NAS treatment
  - Preterm infants require shorter courses of therapy
NAS

Why?

- Cytochrome P450 system is immature in preterm neonates
- Delays metabolism and prolongs half-life of methadone
- Premature birth may decrease the amount of opiate infant is exposed to
- Placental transfer increases in the third trimester
To Detox or Not Detox
To Detox or Not Detox

To Date, the mantra has been NO DETOX

- 1973 article by Rementeria and Nunag reported stillbirth following acute narcotic withdrawal at term

- 1975 Zuspan et al identified elevated amniotic fluid epinephrine levels in a woman undergoing methadone detox
To Detox or Not Detox

- There is actually limited research on the subject

- At OSU we routinely evaluate people for detox
<table>
<thead>
<tr>
<th>Stage of Withdrawal</th>
<th>Symptoms of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipatory (3 to 4 hours after last use)</td>
<td>Fear of withdrawal, Anxiety, Drug-seeking behavior</td>
</tr>
<tr>
<td>Early (8 to 10 hours after last use; for short-acting opioids such as heroin)</td>
<td>Anxiety, Restlessness, Yawning, Nausea, Sweating, Nasal stuffiness, Rhinorrhea, Lacrimation, Dilated Pupils, Stomach cramps, Drug-seeking behavior</td>
</tr>
<tr>
<td>Fully Developed (1 to 3 days after last use, for short-acting opioids, such as heroin)</td>
<td>Severe anxiety, Tremor, Restlessness, Piloerection, Vomiting, diarrhea, Muscle spasm, Muscle pain, Increased blood pressure, tachycardia, Fever, chills, Impulse-driven, drug-seeking behavior</td>
</tr>
</tbody>
</table>

To Detox or Not Detox

The largest single study of pregnant opiate dependent patients

Retrospective case series of 101 patients who underwent a 21-day inpatient opiate detoxification with methadone
To Detox or Not Detox

- Compared results of miscarriage and preterm delivery to published rates of miscarriage and preterm delivery in the standard population

- 1 miscarriage in 5 women undergoing in detox in the first trimester, no losses in second trimester and one PTD in the third trimester
To Detox or Not Detox

Effectiveness

- 50% completed detox, and 1 patient remained drug free at delivery
- Dashe, et al reported on 34 opiate dependent women, enrolled in 12 day detox
- 59% successfully detoxed and did not relapse, 29% resumed antenatal opiate use, 12% did not complete the program
Is there an alternative to methadone?
Buprenorphine

- **Subutex, Suboxone**
  - Suboxone is Buprenorphine/Naloxone

- Synthetic opioid, partial mu-agonist
  - Less severe withdrawal/less euphoria

- Sublingual, daily dosing

- Unlikely teratogenic
Buprenorphine has a very high affinity for mu receptors, thereby displacing morphine, methadone, and other full agonist opioids from the receptor. It has sufficient agonist properties that opioid-addicted persons perceive a subjective effect when they receive an acute dose. These mild subjective effects aid in maintaining compliance with buprenorphine dosing.

Buprenorphine dissociates slowly from the mu receptor, and thus it is able to block the effects of other opioids, such as heroin. Therefore, it is difficult for opioid agonists, such as heroin, to displace buprenorphine and provide further activation of the receptor. Similarly, it is difficult for opioid antagonists, such as naloxone, to displace buprenorphine and precipitate withdrawal.
Buprenorphine

- Used routinely, especially in Europe, for opiate addiction

- Minimal autonomic signs of opiate withdrawal following abrupt cessation of buprenorphine in the adult population
Buprenorphine and Pregnancy

- Buprenorphine maintained pregnancies tend to have same maternal benefit

- NAS associated with buprenorphine appears less severe
Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenorphine substitution

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- Largest prospective observational study of 260 infants
- 49% had good prenatal care
- 96% home with parents
Buprenorphine and pregnancy

- Maximum NAS score similar to methadone
- Mean age at maximum NAS score significantly earlier than methadone
- 16 day mean duration of treatment
- Mean age at recovery of birthweight significantly earlier in buprenorphine
Buprenorphine and pregnancy

- Maximum NAS score similar to methadone
- Mean age at maximum NAS score significantly earlier than methadone
- 16 day mean duration of treatment
- Mean age at recovery of birthweight significantly earlier in buprenorphine
Buprenorphine and pregnancy

- No relationship between buprenorphine dose and severity of NAS was identified.

- In this cohort, buprenorphine and methadone behaved quite similarly.
Buprenorphine vs Methadone

- 3 randomized controlled trials

Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome

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Buprenorphine versus Methadone

- Jones, et al, 2005
  - Compared NAS in neonates of methadone and buprenorphine mothers
  - Double-blind, double-dummy
  - 10 buprenorphine mothers, 11 methadone mothers
Buprenorphine vs Methadone

- 20% of Buprenorphine vs 45% Methadone babies treated for NAS (p=0.23).
- Total amount of medication used to treat NAS babies 1/3 as much in buprenorphine versus methadone (p=0.13)
- Length of stay 1.3 days shorter for buprenorphine (p=0.021)
- Peak NAS scores same between groups (p=0.25)
Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study

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Departments of Psychiatry,¹ Neonatology² and Gynaecology,³ Medical University of Vienna (MUW) and Institute of Psychology, University of Vienna, Vienna, Austria⁴

- Addiction, 2006
- Double-blinded, double-dummy
- N=18, 14 available for analysis
- NAS required treatment in 8, with similar medication needs and length of treatment for both groups
Buprenorphine vs Methadone

Binder and Vavrinkova, Neuroendocrinology Letters, Feb 2008

- 147 IV heroin users
- 30 lost to follow up, 47 remained on heroin, 38 and 32 randomized to buprenorphine and methadone respectively
- NAS most severe and prolonged in babies of methadone mothers
Buprenorphine vs Methadone

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O’Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.
Buprenorphine VS Methadone

RESULTS

Treatment was discontinued by 16 of the 89 women in the methadone group (18%) and 28 of the 86 women in the buprenorphine group (33%). A comparison of the 131 neonates whose mothers were followed to the end of pregnancy according to treatment group (with 58 exposed to buprenorphine and 73 exposed to methadone) showed that the former group required significantly less morphine (mean dose, 1.1 mg vs. 10.4 mg; P<0.0091), had a significantly shorter hospital stay (10.0 days vs. 17.5 days, P<0.0091), and had a significantly shorter duration of treatment for the neonatal abstinence syndrome (4.1 days vs. 9.9 days, P<0.003125) (P values calculated in accordance with prespecified thresholds for significance). There were no significant differences between groups in other primary or secondary outcomes or in the rates of maternal or neonatal adverse events.
Patient dependent on short-acting opioids?

Yes

Withdrawal symptoms present 12 to 24 hrs after last use of opioids?

No

Stop; not dependent on short-acting opioids

Yes

Give buprenorphine/naloxone 4/1 mg, observe 2+ hours

Withdrawal symptoms continue or return?

No

Withdrawal symptoms return?

No

Daily dose established

Yes

Repeat dose up to maximum 8/2 mg for first day

Withdrawal symptoms relieved?

No

Manage withdrawal symptomatically

Yes

Daily dose established

Return next day for continued induction. Review Exhibit 11-5: Induction Day 2
Opiate Addiction in Pregnancy

- Optimal Management
- Multidisciplinary
  - OB/GYN, Psychiatry,
  - Pediatrics
  - Addiction Specialists
  - Nurse Practitioners,
  - Drug Counselors,
  - Social Workers
Opiate Addiction and Pregnancy

- Maintenance vs Detox
- Buprenorphine vs Methadone
- Low Dose vs High Dose
- Inpatient vs Outpatient