2018 ANNUAL MEETING

SUNDAY PRESENTATIONS:

OPIOID USE DISORDER COURSE

North Carolina Obstetrical and Gynecological Society and NC Section of ACOG

April 20-22, 2018 | Omni Grove Park Inn Resort | Asheville, NC

This continuing medical education activity is jointly provided by the American College of Obstetricians and Gynecologists.
Module III

Special Populations
In this module we will review...

- Adolescents and young adults
- Medical co-morbidities
- Psychiatric co-morbidities
- Buprenorphine for the general OB/GYN (or other women’s healthcare provider)
- Managing pain
Adolescents and Young Adults
Use of Pharmacologic Treatment with Adolescents

- Pharmacologic therapy is recommended for all adolescents with severe opioid use disorder

- Buprenorphine is considered first line treatment
  - Most methadone clinics cannot admit patients under 18 years old, though methadone may be a good option for young adults with unstable living arrangements as daily visits provide structure and eliminate the need to manage medications at home
  - Naltrexone is also an option for adolescents and also may be clinically useful for adolescents/young adults living away from home, or patients with co-occurring alcohol use disorders
Treatment Duration

- The optimal length of time for medication treatment is not known
  - Studies in adults have found that patients continued to improve over the course of the first 6 years of treatment
  - However, the impact of exposure to long term agonists/antagonists on the developing brain are unknown
Confidentiality
Tips on “Breaking News” to Parents

- If an adolescent asks for help in disclosing a SUD
  - Choose words that are acceptable to the teen and convey the message accurately. “Pain meds” may be preferable to “narcotics”
  - Share diagnosis and treatment plan; avoid details from the history
  - Support self-efficacy by congratulating the teen on recognizing his/her problem and seeking help

- Support parents who may be shocked and disappointed
  - Focus on the positive: treatment-seeking behavior
  - Reassure that you can help
  - Redirect if a parent becomes very angry or invasive
  - If necessary, ask everyone to calm down before leaving the office
Medical Co-Morbidities
Background

- Persons with opioid use disorders frequently have or at risk of other comorbid medical conditions
- Office-based buprenorphine treatment provides an opportunity to combine substance use treatment with medical care
Hepatitis C virus infection

*The silent epidemic*

- Most common blood-borne infection in U.S., 3.2 million people
  - 70-90% PWID; ~30% <age 30
- 40-60% of chronic liver disease
  - Leading indication for liver transplantation
- HCV-related deaths outnumber deaths due to HIV
Recommended Testing Sequence for Identifying Current HCV Infection

- **HCV Antibody**
  - **Nonreactive**
    - **Not Detected**
      - No HCV antibody detected
      - Additional testing as appropriate
      - STOP
  - **Reactive**
    - **Not Detected**
      - No current HCV infection
      - Additional testing as appropriate
    - **Detected**
      - Current HCV infection
      - Link to care

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
Natural history of HCV infection, variability from person to person

Rising Cure Rates for Chronic HCV (G1)

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN</th>
<th>IFN/RBV</th>
<th>PegIFN/RBV</th>
<th>Telaprevir or Boceprevir + PegIFN/RBV</th>
<th>PR/SMV PR/SOF</th>
<th>IFN-Free DAA Combination Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1998</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td>70-80%</td>
<td></td>
<td>80-90%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>2013</td>
<td></td>
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<tr>
<td>2014+</td>
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</tbody>
</table>

Cure Rate*

HIV Treatment

Today’s combination antiretroviral therapy: less toxic, fewer pills, higher genetic barrier to resistance

Goals of HIV care:
- Improve individual health outcomes
- Restore health, prolong life in a manner indistinguishable from uninfected persons
- Lower community viral load and HIV transmission to achieve an “AIDS-free generation”
Buprenorphine and HIV Outcomes

HIV-infected patients treated with office-based bup/nx in the Buprenorphine-HIV Evaluation and Support (BHIVES) national demonstration project:

- Decreased opioid use
- Increased HIV ART use
- Experienced higher quality of HIV care
- Reported better quality of life

Psychiatric Co-Morbidities
Induced vs Independent Disorder

- Distinguish between substance-induced disorders versus independent psychiatric disorders
  - **Substance-induced:** Disorders related to the use of psychoactive substance; typically resolve with sustained abstinence
  - **Independent:** Disorders which arise during times of abstinence; use of psychoactive substances not the etiology
Substance Induced Psychiatric Disorders

- Patient’s history suggests symptoms occur only when he/she is actively using substances.
- Symptoms are related to intoxication, withdrawal, or ongoing neurobiologic perturbation from substances.
- Onset and/or offset of symptoms are preceded by increases or decreases in substance use.
- Goal should be sustained abstinence followed by re-evaluation of symptoms.
Substance Independent Psychiatric Disorders

- Earliest psychiatric symptoms often precede onset of substance use disorder
- Patient’s history suggests symptoms occur during periods when not using psychoactive substances
- May also find a family history of the disorder
- Goal of substance use disorder treatment should still be cessation of substance use, but treatment must also address psychiatric symptoms simultaneously
General Treatment Principles

- Patients with opioid use disorder and independent depressive, anxiety, or stress disorders
  - Can respond to medication and/or psychotherapy treatments for depression, anxiety, and PTSD
  - Anxiety disorders and PTSD typically treated with antidepressants
- Generally avoid use of benzodiazepines
  - Risk of misuse
  - Possibility of interactions with buprenorphine
Buprenorphine and Benzodiazepines

- Among 34 reported buprenorphine-associated overdoses in France, 31 also had benzodiazepines

- Risks of benzodiazepines
  - Tolerance and withdrawal
  - Excess sedation and falls
  - Cognitive impairment
  - Reinforcement/reward/addiction

- Advantages of benzodiazepines
  - Rapid elimination of anxiety symptoms or insomnia when used short term

Buprenorphine and the General Ob/Gyn
Patients

- L.K. 29 y/o G2P0 schoolteacher at 7 weeks with history of chronic pelvic pain presumed to be secondary to endometriosis. On oxycodone extended-release 20 mg bid given to her by pain specialist. Also history of depression on venlafaxine XR 150 mg

- Per patient, she was told to stop oxycodone extended-release and wean off venlafaxine by genetic counselor/MFM consult
W.S.

- 25 y/o G3P2 at 16 weeks referred because of illicit extended release oxycodone use
- Pt started use about 3 years ago because of low-back pain, but then noticed that it helped her deal with life
- Currently using between 30-120 mg a day. Attempted to stop, but after two days had extreme nausea/vomiting/diaphoresis
Substance Use Disorder

- ASAM “primary, chronic, and neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.” The five Cs:
  - Craving
  - Compulsive use
  - Continued use despite harm (consequences)
  - Impaired control over drug use
  - Chronicity (see above)
- Inability to fulfill work and social obligations
- Use in dangerous situations (drunk driving)
- Legal problems
- Interpersonal problems
Definitions

- **Physical dependence** is defined as “a state of adaptation that often includes tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist”
- Tolerance - need for more drug to obtain same effect
- Withdrawal - adverse physical effects secondary to abruptly stopping use
  - Occur in any patient exposed repeatedly to an opiate or stimulant
- Not a marker of SUD if prescribed
So, do these patients have use disorders?

<table>
<thead>
<tr>
<th>Patient #1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>No</td>
</tr>
<tr>
<td>Compulsive use</td>
<td>No</td>
</tr>
<tr>
<td>Continued use despite harm</td>
<td>No</td>
</tr>
<tr>
<td>(consequences)</td>
<td></td>
</tr>
<tr>
<td>Impaired control over drug use</td>
<td>No</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Yes</td>
</tr>
</tbody>
</table>
So, do these patients have use disorders? (continued)

<table>
<thead>
<tr>
<th>Patient #2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>Yes</td>
</tr>
<tr>
<td>Compulsive use</td>
<td>Yes</td>
</tr>
<tr>
<td>Continued use despite harm (consequences)</td>
<td>Yes</td>
</tr>
<tr>
<td>Impaired control over drug use</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Demographics – Prescription Drug Abuse

- Non-medical use of prescription pain medications increased in those ages 18-25 (and younger)
- More people started using prescription pain meds than marijuana or cocaine (NDSUH, 2006)
- More than half women
- Average age 25
- Narcotic analgesics such as hydrocodone, oxycodone, and methadone more likely to cause overdose death than either heroin or cocaine (Maxwell, 2006)
- Prescription opioids were present in 44% of opioid-related deaths in women (Hall, 2009)
Demographics – Chronic Pain

- 15-20% population severe chronic pain at some point
- 15-20% of people with chronic pain have underlying addictive process
- Up to 40% of patients given opioids for chronic pain develop a use disorder
- Most predictive of risk is personal or family history of alcoholism or other addiction (Chou, 2009)
- Women were more likely than men to report use of any prescription opioid (29.8% females vs. 21.1% males, p<0.001) (Green, 2009)
- Women more likely to be given opioids for pain and higher doses (Cicero, 2009)
Pain Management

- Untreated pain can lead to depression, substance abuse, lost productivity
- Opiates for use in chronic pain controversial
- Huge increase in overdose deaths
- Overdose deaths outnumber deaths by MVA
- IR and ER forms are going under federal regulation
- CDC new guidelines
- With increased regulation, seeing increased heroin usage
  - Cheaper and easier to obtain
Opioids and Chronic Pain

- Women more likely to get opioids for
  - Fibromyalgia
  - Headache
  - Osteoarthritis
- Not effective in any of these
- Up-regulate pain receptors, leading to increased pain
- Women at risk for opioid-induced endocrinopathy (Daniell, 2008)
  - Irregular menses
  - Infertility
Addiction Behaviors Checklist Part 1

<table>
<thead>
<tr>
<th>Addiction behaviors – since last visit</th>
<th>Y</th>
<th>N</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient used illicit drugs or evidences problem drinking</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>2. Patient has hoarded meds</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>3. Patient used more narcotic than prescribed</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>4. Patient ran out of meds early</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>5. Patient has increased use of narcotics</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>6. Patient used analgesics PRN when prescription is for time limited use</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>7. Patient received narcotics from more than one provider</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>8. Patient bought meds on the streets</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Addiction Behaviors Checklist Part 2

<table>
<thead>
<tr>
<th>Addiction behaviors – within current visit</th>
<th>Y</th>
<th>N</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient appears sedated or confused (e.g., slurred speech, unresponsive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patient expresses worries about addiction</td>
<td></td>
<td></td>
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<tr>
<td>3. Patient expressed a strong preference for a specific type of analgesic or a specific route of administration</td>
<td></td>
<td></td>
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<tr>
<td>4. Patient expresses concern about future availability of narcotic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. Patient reports worsened relationships with family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Patient misrepresented analgesic prescription or use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Patient indicated she or he “needs” or “must have” analgesic meds</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Addiction Behaviors Checklist Part 2 (continued)

<table>
<thead>
<tr>
<th>Addiction behaviors – within current visit</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Discussion of analgesic meds was the predominant issue of visit</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>9. Patient exhibited lack of interest in rehab or self-management</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>10. Patient reports minimal/inadequate relief from narcotic analgesic</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>11. Patient indicated difficulty with using medication agreement</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>

Other

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Significant others express concern over patient's use of analgesics</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>
Assessment of Addiction

- Med seeking behavior
- Differentiate addiction from “pseudoaddiction”
  - e.g., hoarding meds and asking for refills early could be sign of undertreated pain
  - Some group as part of problematic or aberrant behaviors
- Women less likely to set limits on themselves when dealing with pain and use opioids to help them continue to be productive
- Think about diversion
Methadone and Chronic Pain

- Physicians can prescribe for chronic pain and for patients with use disorders while in the hospital (for another medical indication)
- 213 percent increase in methadone related overdose deaths between 1999-2003 associated with use in pain and not in treatment centers
- Also methadone can prolong QTc and precipitate sudden cardiac death, especially in conjunction with other medications that prolong QTc
Advantages of Buprenorphine

- Don’t have to go to special center for daily dosing
- Less risk of diversion
- NAS less severe than methadone
- Not indicated for treatment of chronic pain, but being used off label.
- Being studied now, anecdotally very effective for certain patients and with chronic pelvic pain which traditionally not well treated with methadone
L.K. (continued)

- Counseled on pain control, weaning, etc.
- Able to wean down to 10 mg every other day, but not able to stop (Pain improved with pregnancy)
- Baby born full term, no NAS
- Breast fed for 1 ½ years
- Pain med needs continued to increase after pregnancy (up to 60 mg bid with hydrocodone/acetaminophen for “breakthrough pain”)
- Amenorrheic
- Hospitalized for severe depression. Admitted to chewing oxycodone extended release for high
Co-Occurring Disorders

- As many as 2/3 women with substance use disorders have co-occurring mental health disorders
  - Depression
  - Anxiety
  - PTSD
- More likely than men to have depression and anxiety
- Up to 80% have history of childhood sexual trauma/IPV
- Treatment must account for preconception issues in women of childbearing age
  - SSRIs, mood stabilizers, benzodiazepines
L.K. (continued)

- Switched to bup/nlxn. Pain better controlled
- Counseling/therapy for severe PTSD
- SSRI-fluoxetine 100 mg
- Quit smoking
- Menses return and she gets pregnant (planned and desired)
- During pregnancy has hepatitis flare.
  - Chronic congenital hepatitis b infection, stopped tenofovir during pregnancy
- Baby born at 37 weeks (cholestasis of pregnancy) by C-section for breech
- Didn’t breast feed (pediatrician didn’t feel comfortable with the tenofovir)
- Baby without NAS
W.S.

- Uneventful induction onto buprenorphine while pregnant
- Delivered at term
- Healthy baby. No NAS
- Still my patient 7 years later 2 relapses
  - Oxycodone x 6 months
  - Meth-brief
- 1 unintended pregnancy-TAB with LNG IUS
- 1 planned uncomplicated pregnancy with term delivery
  - Another LNG IUS
Contraception

- LARC obviously ideal in this population
- Consider immediate postpartum insertion
- Should be addressed frequently
- If not on adequate contraception, should be on folic acid supplementation
  - Preconception opioids and 1st trimester use may be associated with increased risk of neural tube defects
Smoking Cessation

- 51% of people with a history of addiction treatment die of smoking-related causes
- 1.5 X the rate of addiction-related causes
- 63% of all women in addiction treatment smoke cigarettes
- Traditionally not addressed in SA treatment “we’ll work on one thing at a time.”
- Smoking cessation increases abstinence from drug use

SAMHSA 2011, Lemon 2003
SBIRT

- Screening, brief intervention, referral to treatment
- Need universal screening of all women of childbearing age
  - Screening tools-4Ps, NIDA quick screen
  - Conversation, not just the tool
  - Not urine drug monitoring
Pregnancy
Neonatal Abstinence
Breastfeeding
Objectives

At the end of this presentation, participants should be able to:

- Describe the risk/benefit of detoxification from opioids during pregnancy versus medical assisted therapy for the treatment of opioid dependence during pregnancy
- Describe the elements of the multidisciplinary team during pregnancy
- Describe the approach to intrapartum and postpartum pain management during
Options for opioid dependence during pregnancy

- Detoxification
- Methadone
- Buprenorphine
Pregnancy: Initial Evaluation

- Know about specialized treatment services available in the community for pregnant, opioid-dependent patients
  - Referral should be made regardless of the patient’s decision to continue the pregnancy
- Obtain consent to talk to her obstetric provider
Why has detoxification from opioids during pregnancy been long avoided?

Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report

José Luis Rementeria, M.D.
Nemesio N. Nunag, M.D.
Bronx, New York

A stillborn infant was born to a drug-addicted mother who had withdrawal symptoms shortly before delivery. Mechanisms are presented to help explain the possible relationship between the maternal withdrawal and the fetal death. Statistics are also presented to show an increased stillborn and neonatal mortality rate in the over-all pregnant drug-addicted population.

There is a fear that any withdrawal will cause fetal harm
Detoxification: Not Best Approach for Maternal Care

- 93 patients
- All offered detoxification
- Gestational age about 20 weeks at entry
- Duration of detoxification: 25 days
- 3 women with fetal demise not counted in statistics: 2 of them failed detox, had no treatment, continued illicit drug use, and presented with IUFD.

42/95 (44%) women were not engaged in treatment, 2 had IUFD

There was no f/u of how the women fared after delivery

Detox can be done: are we treating women only for the benefit of the fetus?

Stewart, AJOG, 2013
Bell et al (2016) reported on 301 patients who underwent detoxification during pregnancy.

No adverse fetal outcomes (2 IUFDs of those acutely detoxed during first trimester).

NAS rates 31% (17-70)

Relapse rates 36% (17-74)

No control group on MAT (Mother Study-NAS rates 47%)

Treating a chronic condition with an acute treatment without clear fetal benefit.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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</thead>
<tbody>
<tr>
<td>Demographics, gestational age at the time of detoxification, neonatal intensive care unit admission, and pregnancy outcome of the opiate detox study population</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Mean maternal age, y</td>
</tr>
<tr>
<td>Maternal age range, y</td>
</tr>
<tr>
<td>Maternal age &lt;30 y</td>
</tr>
<tr>
<td>Multiparity</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>African-American</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age at detoxification and NICU admission</th>
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</thead>
<tbody>
<tr>
<td>Detoxification first trimester, 5−13 wks gestation</td>
</tr>
<tr>
<td>Detoxification second trimester, 14−27 wks gestation</td>
</tr>
<tr>
<td>Detoxification third trimester, ≥28 wks gestation</td>
</tr>
<tr>
<td>Preterm deliveries prior to 37 wks gestation</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of NAS</td>
</tr>
<tr>
<td>Rate of relapse</td>
</tr>
</tbody>
</table>

Group 1 consisted of acute detoxification (unmedicated patients). Group 2 consisted of inpatient detoxification with routine behavioral health follow-up. Group 3 consisted of inpatient detoxification without routine behavioral health follow-up. Group 4 consisted of outpatient buprenorphine detoxification. NAS, neonatal abstinence syndrome; NICU, neonatal intensive care unit.

1 One Hispanic in group 1 and one Asian in group 6.
2 Relapse rate is defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal neonatal NICU test that includes any of the patients who had newborns treated for neonatal abstinence syndrome.

# Pregnancy: Benefits of Opioid Agonist Therapy

<table>
<thead>
<tr>
<th>Maternal Benefits</th>
<th>Fetal Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>70% reduction in overdose related deaths</td>
<td>Reduces fluctuations in maternal opioid levels; reducing fetal stress</td>
</tr>
<tr>
<td>Decrease in risk of HIV, HBV, HCV</td>
<td>Decrease in intrauterine fetal demise</td>
</tr>
<tr>
<td>Increased engagement in prenatal care and recovery treatment</td>
<td>Decrease in intrauterine growth restriction</td>
</tr>
<tr>
<td></td>
<td>Decrease in preterm delivery</td>
</tr>
</tbody>
</table>
Opioid Maintenance Therapy

Methadone versus buprenorphine for the treatment of opioid dependence during pregnancy
Pregnancy: Maintenance Therapy Remains the Standard of Care

- Methadone and buprenorphine (both category C) are safe and effective treatment options in pregnancy
- The decision of which therapy to start is complex and should be individualized for each woman
  - Based on available options, patient preference, patients’ previous treatment experiences, disease severity, social supports, and intensity of treatment needed

Jones et al. 2010.
MOTHER Study

Randomized trial of methadone versus buprenorphine

Primary outcome: NAS
- Similar prevalence of treatment for NAS
- Less neonatal abstinence severity and treatment (bup)
- Shorter neonatal LOS (bup)
- Bigger HC

Jones, NEJM, 2010
MOTHER Study

Secondary outcomes:

- Bigger neonates (bup)
- No difference preterm birth
- Longer gestational age (bup)

Jones, NEJM, 2010
Secondary measures: maternal outcomes

- Fewer medical/delivery complications (bup)
- Increased % of women randomized to buprenorphine did not complete the study

Jones, NEJM, 2010
Incidence of infection was low
No significant difference in any outcome by medication: incidence is rare
Notable all 4 PPROM in methadone (NS)
Notable that women on methadone were more likely to present with preterm labor (15% vs. 2%)
Respiratory distress more frequent in neonates of women treated with methadone (19% vs. 5%) (remember average gestational age 37.9 wks for methadone; 39 weeks for buprenorphine)

Take home: women do quite well with either medication

Holbrook, Addiction, 2012
### Summary of outcomes:

<table>
<thead>
<tr>
<th>Maternal</th>
<th>FAVORS Methadone</th>
<th>EQUIVALENT</th>
<th>FAVORS Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment efficacy</td>
<td><em>better for women that failed treatment in past</em></td>
<td>X*</td>
<td><em>can be considered reasonable first line treatment</em></td>
</tr>
<tr>
<td>Access to treatment</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Requires withdrawal for initiation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment automatically coordinated</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal medical complications</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Long-term outcome: data</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Birthweight</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>% requiring NAS treatment</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Severity of NAS symptoms</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Duration of NAS treatment</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Take Home Message Regarding Methadone and Buprenorphine for the Treatment of Opioid Dependence During Pregnancy

- Methadone or buprenorphine may be used during pregnancy
- It is acceptable care to initiate or maintain women on buprenorphine that meet the criteria and in whom it is the best therapeutic option
- We and many other centers are using buprenorphine routinely for patients presenting for care in whom treatment compliance/access will be improved with buprenorphine
- Buprenorphine may have some benefits over methadone for maternal outcomes; it is certainly not worse compared to methadone
Assemble the Team: It Takes A Village… No Matter the Medication
(And most of us cannot coordinate the village for every patient)
How to Use Buprenorphine in Pregnancy
Management of Buprenorphine Patient: Newly Pregnant

- For women stable on buprenorphine/naloxone who become pregnant:
  - Current standard of care is to switch to buprenorphine monotherapy at the same dose
  - The combination therapy has been avoided due to the unknown exposure risk of naloxone in pregnancy and concern for misuse causing acute withdrawal and fetal distress
  - Becoming standard of care in some areas because of worry for diversion risk
Considerations

- Do women tolerate buprenorphine?
  - Why did the Mother Study have such a high drop out rate (33% vs. 18%)?

- How much withdrawal can a pregnant woman and her fetus tolerate?
Areas of Concern:

- Why was there a high dropout rate of women randomized to buprenorphine in the MOTHER study? (33% buprenorphine; 18% methadone)

- How much withdrawal can a pregnant woman and her fetus tolerate?

Women that discontinued buprenorphine had higher CINA scores in the first 48 hours after induction

Holbrook, Drug and Alcohol Dependence, 2013
Fetal Neurologic System Development: Theoretically, fetal withdrawal should not occur until late in gestation

1st trimester
2nd trimester
3rd trimester

Neuroblast development
5-25 weeks

Glial development
20 weeks through term

Corticospinal tracts and dendritic development
24 weeks through childhood
The Cardiovascular Effects of Moderate Withdrawal Are Well-Tolerated in Pregnancy

Meyer, SMFM, 2014
If We’re So Worried About Withdrawal, How Do We Start Bup?

- Ensure moderate withdrawal before initiating treatment and quickly work to get women comfortable with small incremental dosages
  - CINA 10
  - COWS 12

- Induction from methadone to buprenorphine can be associated with higher rates of dissatisfaction with buprenorphine
  - Methadone long half life
  - Higher rates of precipitated withdrawal

- Pregnant women tolerate the cardiovascular effects of moderate withdrawal well

- Need fetal data
  - Third trimester inductions usually done in hospital

Stable patient <24 weeks

Outpatient induction scheduled

Patient asked to abstain from opioids 12-24 hrs
COWS scoring: treat as increasing above 10-12
Start with buprenorphine 2-4 mg.
If no precipitated withdrawal in 30 minutes, increase rapidly as needed to obtain symptom control

Usual visit 2-3 hours
Follow-up 1-3 days; adjust as outpatient

Unstable patient > 24 weeks

Admission scheduled: anticipated 24-36 hours

Patient asked to abstain from opioids 12-24 hours
Admission to inpatient /triate. Continuous EFM
COWS scoring: Start with score > 10-12
Start with buprenorphine 2-4 mg.
If no precipitated withdrawal in 30 minutes, increase rapidly as needed to obtain symptom control
Occasionally need anxiolytics/sleep medications

Discharge when reasonably stable
Follow-up 1-3 days; adjust as outpatient
Sample Inpatient Nursing Protocol

- Admit for observation
- Obtain NST upon admission, then bid and prn for COWS > 20
- Regular Diet as tolerated
- COWS score q 2hours until buprenorphine initiated
- Give initial dose buprenorphine 4 mg for COWS > 10
- Observe for 60 minutes. If tolerated and COWS > 6, give additional 4 mg. Repeat COWS q hour and give 4 mg prn COWS > 6. Total first day dose usually 12-16 mg. (occasionally can be higher).
- Day 2 dose is total received day 1 given in am after last dose (or at least 8 hours)
- If switching from methadone or other long-acting opioid, start with 2 mg
- Can give fentanyl or additional bup for precipitated withdrawal
- Rarely need to give Z drugs (zolpidem/eszopictone/zaleplon) for sleep
  - Hydroxyzine, diphenhydramine work well
Outpatient Follow-up During Pregnancy

Frequent visits allow for frequent feedback/intervention for noncompliance (we have found this really helpful)

- See patient within 1-3 days after initiation of buprenorphine
- Ask about symptoms (checklist) and counseling (confirm) (if you do not provide OB care, confirm she is receiving care)
- Provide witnessed urine for drug screen
- Provide prescription for 1 week
  Weekly follow-up visit

For patients that have been quite stable and compliant, we reduce frequency to every 2 weeks
Take Home Message About Buprenorphine Inductions

- Induction can occur in the outpatient setting or overnight stay
- Moderate withdrawal symptoms are well tolerated by pregnant women
- The degree of maternal withdrawal may be important in patient satisfaction with medication
- Dosing in smaller incremental doses may be important in patient satisfaction with medication
- Medication will need to be adjusted frequently for induction and over the course of pregnancy
Withdrawal Symptoms By Visit:
Complaints are frequent; more so when buprenorphine initiated during pregnancy

Key:
- **Yellow**: Buprenorphine initiated prior to conception (n=18)
- **Green**: Buprenorphine initiated during pregnancy (n=28)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Craving</th>
<th>Sweating</th>
<th>Laceration</th>
<th>Runny Nose</th>
<th>Gooseflesh</th>
<th>Yawning</th>
<th>ABD pain</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>(of visits per patient, n=244 visits)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

75
% Requiring Dose Change by Trimester:
About 2/3 of women on a stable dose prior to pregnancy will need an increase in dose during gestation

![Bar chart showing percentage of women requiring dose change by trimester.](chart.png)

**Key:**
- Buprenorphine initiated prior to conception (n=18)
- Buprenorphine initiated during pregnancy (n=28)
Dose Change by Trimester:
The largest dose changes occurred in the second trimester.
Pregnancy change modest in previously stable patients: 4-6 mg
Fetal Assessment in Women Treated With Methadone or Buprenorphine

Patients:
- MOTHER study
- Maintained on methadone or buprenorphine (blinded)
- BPP/NST 2 hrs prior to a dose; repeated 2 hrs after the dose (peak effect)

<table>
<thead>
<tr>
<th></th>
<th>Predose NST</th>
<th>Postdose NST</th>
<th>Predose BPP</th>
<th>Postdose BPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>No difference than pre-dose</td>
<td>More likely non-reactive than pre-dose</td>
<td>No difference*</td>
<td>Both meth and bup: Significant chance reduced movement; Non-sig increased chance of no breathing</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>More likely reactive than methadone</td>
<td>*if pre- and post-scores are combined, bup BPP scores higher (8.7± vs 8.2±0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*if pre- and post-scores are combined, bup BPP scores higher (8.7± vs 8.2±0.2)

Interpret antenatal testing cautiously when a few hours after a dose

Salisbury, Addiction, 2012
Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

- Generalized disorder with dysfunction of the autonomic nervous system, GI tract and respiratory system
- Occurs in 60-80% of infants with intrauterine exposure to opioid maintenance therapy
- Onset: majority present within 72 hours after delivery
- Duration: up to 4 weeks (prolonged if exposed intrauterine to more than one substance associated with NAS)
Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

- Meta-analysis of 12 studies from 1996-2012: showed buprenorphine exposed neonates (515) compared to methadone exposed (855) had
  - Shorter mean length of hospital stay (-7.23 days, 95% CI: -10.64, -3.83)
  - In treated neonates, buprenorphine exposed
  - Shorter NAS treatment duration(-8.46 days, 95% CI: -14.48, -2.44)
  - Lower morphine dose (-3.60 mg, 95% CI: -7.26, 0.07)

Brogly et al. 2014.
Maternal Dose and NAS Severity

- No correlation between maternal opioid maintenance therapy dose and the duration or severity of NAS
- Women should be encouraged to report any symptoms of withdrawal through her pregnancy without fear a dose increase will affect her baby’s hospital stay or need for NAS treatment

Opioid Use Disorder and Breastfeeding

- The transfer of methadone and into human milk is minimal and unrelated to maternal doses
- Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
  - The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- Both are considered Category L3 (probably compatible)

Breastfeeding and NAS

- Benefits of breastfeeding for newborns with NAS
  - 30% decrease the development of NAS
  - 50% decrease in neonatal hospital stay
  - Improved mother-infant bonding
  - Positive reinforcement for maternal recovery

Tobacco Use Contributes to Poor Outcomes of All
Doctor, is there ANY way to reduce the chance my baby will have withdrawal?

Jones HE, Drug and Alcohol Dependence, 2013
Summary of Pregnancy Specific Considerations to Buprenorphine Therapy

- Assess the patient for the best overall treatment plan and recommend medication based on the overall patient needs, not specifically a medication
  - Buprenorphine can be considered first line in patients for whom office based therapy is appropriate
  - Document opioid dependence and increase dose incrementally during induction
- Develop the team approach, obtain the needed consents for free flow of information among the team
  - Medication provider, obstetrics, pediatrics, social work, community based support/nursing
- When antenatal testing is indicated based on standard obstetric indications, try to test patients either early in the day before a dose or in the afternoon hours after a dose
- Encourage smoking cessation/reduction
“Labor is a natural process necessarily attended with more or less violence......it involves exertion which is associated with more or less suffering....”

Barton Hirst MD, System of Obstetrics, 1888
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
- How should post-op pain be managed?

Alford, Annals Int Med 2006
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
  - No: it will create the potential for term withdrawal and relapse, which we have tried to avoid through pregnancy
  - Reasonable to continue whatever medication for opioid dependence to avoid withdrawal

- Does regional analgesia work?
- How should post-vaginal delivery pain be managed?
- How should post-op pain be managed?

Alford, Annals Int Med 2006
Common Analgesia Questions: Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
  - Yes
- How should post-vaginal delivery pain be managed?
- How should post-op pain be managed?

Alford, Annals Int Med 2006
# Efficacy of Neuraxial Analgesia: Similar

<table>
<thead>
<tr>
<th></th>
<th>Methadone N=36</th>
<th>Control N=35</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain before NA</td>
<td>9 (8, 10)</td>
<td>9 (7.5, 10)</td>
<td>0.86</td>
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<tr>
<td>Pain after NA</td>
<td>1 (0, 3.3)</td>
<td>1.3 (0, 2)</td>
<td>0.77</td>
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<tr>
<td>PCEA settings</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal (cc/hr)</td>
<td>11.7± 1.7</td>
<td>10.6 ± 1.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Delay</td>
<td>6.6 ± 1.9</td>
<td>6.1 ± 1.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Bolus</td>
<td>8.0 ± 2.8</td>
<td>8.0 ± 2.5</td>
<td>0.96</td>
</tr>
<tr>
<td>1 hour max infusion</td>
<td>34.6 ± 1.6</td>
<td>34.0 ± 3.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Extra bolus needed during labor</td>
<td>11 (30.6)</td>
<td>4 (11.4)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
## Efficacy of Neuraxial Analgesia: Similar (Maybe more epidural boluses)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain before NA</strong></td>
<td>9 (8, 10)</td>
<td>8.8 (8, 10)</td>
<td>0.74</td>
</tr>
<tr>
<td>N=39</td>
<td>N=42</td>
<td></td>
<td></td>
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<tr>
<td><strong>Pain after NA</strong></td>
<td>2 (0, 3.6)</td>
<td>2 (0.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>N=34</td>
<td>N=41</td>
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</tbody>
</table>

### PCEA settings* (Stand Sol: 1/6% bupivacaine + 1 mcg fentanyl/cc)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal (cc/hr)</strong></td>
<td>10.1±0.6</td>
<td>10.1±0.7</td>
<td>0.60</td>
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<tr>
<td>N=46</td>
<td>N=42</td>
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<tr>
<td><strong>Delay</strong></td>
<td>7.8±3.2</td>
<td>9.5±1.5</td>
<td>0.007</td>
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<tr>
<td>N=46</td>
<td>N=42</td>
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<tr>
<td><strong>Bolus</strong></td>
<td>6.7±1.6</td>
<td>7.4±1.3</td>
<td>0.02</td>
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<tr>
<td>N=46</td>
<td>N=42</td>
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<tr>
<td><strong>1 hour max Infusion</strong></td>
<td>35.7±1.8</td>
<td>35.8±1.2</td>
<td>0.90</td>
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<tr>
<td>N=46</td>
<td>N=41</td>
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<tr>
<td><strong>Extra bolus needed during labor</strong></td>
<td>19/46 (30.6)</td>
<td>8/43 (11.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Data omits: one case that had no relief from the epidural and it was felt to be in the wrong space; patient received spinal with good relief; two controls that received epidural but delivered prior to starting PCEA

**not normalized to duration of epidural (yet)
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
  - Similar to other patients: access to short acting opioids
- How should post-op pain be managed?

Alford, Annals Int Med 2006
Postpartum Vaginal Delivery Opioid Use and Pain Score: 24 hrs PP:

Women treated with methadone or buprenorphine have more pain

Meyer, Ob Gyn 2007; Euro J Pain 2010
Common Analgesia Questions: Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
- How should post-op pain be managed?
  - IV and short acting opioids
  - Consider split dose of maintenance medication
  - PCEA x 24 hrs if severe, intractable pain

Alford, Annals Int Med 2006
Postoperative Cesarean Delivery, Opioid Use and Pain Score: 70% More Opioid Required

Meyer, Ob Gyn 2007; Meyer Euro J Pain 2010
AVOID AGNOIST/ANTAGONISTS:

- Nalbuphine
- Butorphanol
ALERT:
Nalbuphine and butorphanol are partial opioid agoists and can precipitate acute withdrawal in opioid dependent patients

Patient maintained on methadone requested medication for pain
Received nalbuphine 10 mg IV

- Physical Exam
  - Agitated, crying, c/o severe abdominal cramps, muscle cramps- worse in legs, cold w/ shaking chills, tremulous
  - RR subjectively increased no vitals recorded
  - Abd S/NT, fundus soft, ↑BS
- Fetal Tachycardia
Received IV morphine

- Fetal Tachycardia continued x 45min., with subsequent return to baseline
  - No decelerations
Overall Pain Management Approach:
Continue long-acting opioid agonist for treatment of opioid dependence

Present in labor requesting something for pain

Consider either full agonist opioid (NO nalbuphine or butorphanol)
Or
Offer regional analgesia (expect good response to initial placement; may need additional boluses)

Vaginal birth

Routine postpartum orders with prn opioid analgesics x24 hrs

Cesarean birth

First 24 hrs: anticipate increased needs, consider morphine or hydromorphone PCA; consider PCEA; consider TAP if you anesthesia department does them

after 24 hrs: increased potency short acting opioid (hydromorphone) with 50-70% increased dose (4-6 mg po q4-6 hrs); duration of treatment similar
Breastfeeding
Both Buprenorphine and Naloxone Are Compatible With Breastfeeding

Summary of Use during Lactation:
Because of the low levels of buprenorphine in breastmilk, 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. Monitor the infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants. Although unlikely, if the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately. Observe infants for withdrawal signs if breastfeeding is stopped abruptly. The breastfeeding rate among mothers taking buprenorphine for opiate addiction may be lower than in other mothers.

Summary of Use during Lactation:
No information is available on the excretion of naloxone into breastmilk. Because it is not orally bioavailable, it is unlikely to affect the breastfed infant. Studies in nursing mothers have shown that naloxone does not affect lactation hormone levels. If naloxone is required by the mother, it is not a reason to discontinue breastfeeding.

Buprenorphine
CASRN: 52485-79-7

Naloxone
CASRN: 465-65-6
Not Convinced? Look at oxycodone and breastfeeding (Codeine is worse)

Oxycodone
CASRN: 76-42-6

Summary of Use during Lactation:
Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, central nervous system depression and even death. Infant sedation is common and well documented with maternal use of oxycodone. Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of oral oxycodone (and combinations) to a few days. A maximum oxycodone dosage of 30 mg daily is suggested. Oxycodone elimination is decreased in young infants with much inter-individual variability. Monitor the infant closely for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately. Other agents are preferred over oxycodone during breastfeeding.
Assemble the Team: It Takes A Village... No Matter the Medication
(And most of us cannot coordinate the village for every patient)
What About Non-Ob Pain?
Altered Pain Experience

- In experimental pain studies...
  - Patients with active opioid use disorder have less pain tolerance than peers in remission or matched controls
  - Patients with a h/o opioid use disorder have less pain tolerance than siblings without an addiction history
  - Patients on opioid maintenance treatment (i.e. methadone, buprenorphine) have less pain tolerance than matched controls

- Which came first?
  - Opioid use disorder or less pain tolerance?

“Opioid Debt”

- Patients with an opioid use disorder who are physically dependent on Opioid Agonist Treatment (i.e. methadone or buprenorphine) must be maintained on a daily equivalence before ANY analgesic effect is realized with opioids used to treat acute pain.
- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance.

Acute Pain
Buprenorphine Maintenance Treatment

Theoretical Concern

- May antagonize effects of previously administered opioids
- May block the effects of subsequent administered opioids
- However...Experimental mouse and rat pain models
  - Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl) resulted in additive or synergistic effects
  - Receptor occupancy by buprenorphine does not appear to cause impairment of mu-opioid receptor accessibility

Acute Pain

Buprenorphine Maintenance Treatment Options

- Continue buprenorphine and titrate short-acting opioid analgesic
- D/c buprenorphine, use opioid analgesic, then re-induce
- Divide buprenorphine to every 6-8 hours
- Use supplemental doses of buprenorphine*
- **If inpatient,**
  - D/c buprenorphine
  - Start methadone 20-40mg (or other long-acting opioid) for opioid debt
  - Use short-acting opioid analgesics
  - Then re-induce w/ buprenorphine when acute pain resolves

Chronic Pain
Buprenorphine Maintenance Treatment

- Systematic review
- 10 trials involving 1,190 patients
- Due to heterogeneity of studies, pooling results and meta-analysis not possible
- All studies reported effectiveness in treating chronic pain
- Majority of studies were observational and low quality
- Current evidence insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain
- Expert opinion supports the use of buprenorphine for chronic pain in patients diagnosed with an opioid use disorder
- Needs to be dosed q6-8 hours. May not have a ceiling effect for pain

Cotes, J; Montgomery, L. Pain Medicine. 2014.
Overdose Prevention

- Naloxone should be prescribed to everyone with an opioid use disorder
- Pregnant women should receive naloxone in cases of overdose to prevent death to mother and fetus
- Available formulations
- Families also need to have it available
Providers’ Clinical Support System
For Medication Assisted Treatment

What We Do
We are a national training and mentoring project developed in response to the prescription opioid misuse epidemic and the availability of newer pharmacotherapies to address opioid use disorder. The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

View Modules
The foundation for provider education on topics related to medication-assisted treatment for opioid use disorder.
Start Training

Find a Mentor
The mentor program provides individualized support and mentoring for providers treating opioid use disorder.
Connect Now

Watch Webinars
Webinars provide expanded education targeted at clinicians engaged in the treatment of opioid-dependent patients.
Watch Now
PREGNANCY:
Methadone and Buprenorphine

Some women are surprised to learn they got pregnant while using heroin, OxyContin, Percocet or other pain medications that can be misused (known as opioid drugs). You, along with family and friends, may worry about your drug use and if it could affect your baby.

Some women may want to “detox” as a way to stop using heroin or pain medicines. Unfortunately, studies have shown that 8 out of 10 women return to drug use by a month after “detox.” Therefore, most doctors now advise patients in pregnant women with methadone or buprenorphine. These are long-acting opioid medications that are associated with improved outcomes in pregnancy.

HOW CAN I GET STARTED ON METHADONE OR BUPRENORPHINE?
- Depending on where you live, there may be a special program that offers care to pregnant women who need methadone or buprenorphine. These programs can offer prenatal care and substance use counseling along with your medication.
- Methadone may only be given by a specialized doctor while buprenorphine may also be available from your primary care physician or obstetrician if they have received special training.
- Some women may prefer to get help from starting their medications while in a residential (inpatient) treatment facility.

WHAT IS THE BEST DOSE OF METHADONE OR BUPRENORPHINE DURING PREGNANCY?
There is no “best” dose of methadone or buprenorphine for all women, and it should be taken under the care of a licensed professional. The goal is to reduce the risk of withdrawal and other complications.

HOW SAFE IS IT TO TAKE METHADONE OR BUPRENORPHINE (SUBSTITUTES) DURING PREGNANCY?

- In the right doses, both methadone and buprenorphine stop withdrawal, reduce craving, and block the effects of other opioids.
- Treatment with methadone or buprenorphine makes it more likely that the baby will grow normally and not come too early.

- Based on many years of research studies, neither methadone has been shown to be less harmful than other opioids.
- Babies born to women who are addicted to heroin or prescription opioids can have temporary withdrawal or addiction symptoms to the baby (Neonatal Abstinence Syndrome or NAS). These symptoms can occur in Babies whose mothers take methadone or buprenorphine.
- Talk with your doctor about the benefits versus the risks of medication treatment along with the risks of not taking medication treatment.

IS METHADONE OR BUPRENORPHINE A BETTER MEDICATION FOR ME IN PREGNANCY?

- A pregnant woman and her doctor should discuss both methadone and buprenorphine. The choice may be limited by which medication is available in your community.
- If a woman is already on methadone or buprenorphine and becomes pregnant, doctors usually advise her to stay on the same medication.
Billing/Coding

- Pregnant women can bill E:M code in addition to global Ob. Usually time-based
- Screening, brief intervention, referral to treatment has separate E:M code
  - 99408 and 99409
  - H0049 and H0050-Medicare
- If not pregnant, again use E:M coding
Questions?
Completing the Waiver Paperwork
BUPRENORPHINE
Waiver Notification Form

Entering a 30 Patient Notification
Submitting a 30 patient Notification form on line

Before you begin
Before starting this application, please make sure you have
- Your DEA Number
- Your State Medical License Number
- Your Training Certificate Information

Do you work for the US military, Veterans Administration, or Indian Health Service?

- Yes  
- No

Answer the question yes or no and click the Next button.
Check your eligibility

• Use the drop down menu to select your licensing state.
• Enter your medical license number, letters and numbers only. No spaces or dashes.
• Enter your DEA number, letters and numbers only.
• Click the Submit button.
Eligible?

The system will indicate the number of patients you are eligible to submit a Notification for. Click the Next button.

The state, medical license and DEA number will be pre-populated.
Complete Notification Form

1A. Enter your name and suffix. (M.D. or D.O.)
1B. Medical license number will be pre-populated
1C. License state will be pre-populated
1D. DEA number will be pre-populated
2. Address – if you are planning to store buprenorphine on-site, you will need to provide the address you are listed under with DEA. Otherwise, you may provide an address in your licensing state. Do not enter a P.O. Box as your street address.

3. Enter phone number

4. Enter fax number

5. Enter email address, twice. Please provide an email address you regularly access. All correspondence from SAMHSA will be via email.
6. Purpose of Notification

The New box will be pre-checked.

7. Check the box, that you will only use approved Schedule III, IV, & V medications.
8. Certification of Qualifying Criteria
Check the appropriate box if you have a sub-specialty in Addiction medicine or psychiatry.
Check the appropriate box for the 8 hour training course you completed.
Enter the date the training was completed.
Enter the city where the training was completed. If you have complete an on-line course type “web” for your city.
The state will be pre-populated but you may change it if it does not correspond with where you complete on site training.
9. Certification of Capacity
   Check box – must certify that you will refer patients for counseling.
10. Certification of Maximum Patient Load – button is pre-populated
11. Consent to Release Contact Information – click the “consent” or “do not consent” button
12. Check the box which states that you have not knowingly given false information.
Type your name in the box as your signature.
Type in your DEA number matching the one you entered initially.
Click the Submit button.
When the Notification is submitted successfully you will receive a confirmation. If it has not, an error message will indicate what needs to be corrected.
Questions? Email education@ASAM.org or call 301.656.3920
Module III

Special Populations
In this module we will review...

- Adolescents and young adults
- Medical co-morbidities
- Psychiatric co-morbidities
- Buprenorphine for the general OB/GYN (or other women’s healthcare provider)
- Managing pain
Adolescents and Young Adults
Use of Pharmacologic Treatment with Adolescents

- Pharmacologic therapy is recommended for all adolescents with severe opioid use disorder

- Buprenorphine is considered first line treatment
  - Most methadone clinics cannot admit patients under 18 years old, though methadone may be a good option for young adults with unstable living arrangements as daily visits provide structure and eliminate the need to manage medications at home
  - Naltrexone is also an option for adolescents and also may be clinically useful for adolescents/young adults living away from home, or patients with co-occurring alcohol use disorders
Treatment Duration

- The optimal length of time for medication treatment is not known
  - Studies in adults have found that patients continued to improve over the course of the first 6 years of treatment
  - However, the impact of exposure to long term agonists/antagonists on the developing brain are unknown
Confidentiality
Tips on “Breaking News” to Parents

- If an adolescent asks for help in disclosing a SUD
  - Choose words that are acceptable to the teen and convey the message accurately. “Pain meds” may be preferable to “narcotics”
  - Share diagnosis and treatment plan; avoid details from the history
  - Support self-efficacy by congratulating the teen on recognizing his/her problem and seeking help

- Support parents who may be shocked and disappointed
  - Focus on the positive: treatment-seeking behavior
  - Reassure that you can help
  - Redirect if a parent becomes very angry or invasive
  - If necessary, ask everyone to calm down before leaving the office
Medical Co-Morbidities
Background

- Persons with opioid use disorders frequently have or at risk of other comorbid medical conditions
- Office-based buprenorphine treatment provides an opportunity to combine substance use treatment with medical care
Hepatitis C virus infection

*The silent epidemic*

- Most common blood-borne infection in U.S., 3.2 million people
  - 70-90% PWID; ~30% < age 30
- 40-60% of chronic liver disease
  - Leading indication for liver transplantation
- HCV-related deaths outnumber deaths due to HIV
**Recommended Testing Sequence for Identifying Current HCV Infection**

- **HCV Antibody**
  - **Nonreactive**
    - No HCV antibody detected
    - STOP*
  - **Reactive**
    - **Not Detected**
      - No current HCV infection
      - Additional testing as appropriate†
    - **Detected**
      - Current HCV infection
      - Link to care

---

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
Natural history of HCV infection, variability from person to person

Rising Cure Rates for Chronic HCV (G1)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cure Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>IFN 16%</td>
</tr>
<tr>
<td>1998</td>
<td>IFN/RBV 35%</td>
</tr>
<tr>
<td>2001</td>
<td>PegIFN/RBV 44%</td>
</tr>
<tr>
<td>2011</td>
<td>Telaprevir or Boceprevir + PegIFN/RBV 70-80%</td>
</tr>
<tr>
<td>2013</td>
<td>PR/SMV PR/SOF 80-90%</td>
</tr>
<tr>
<td>2014+</td>
<td>IFN-Free DAA Combination Regimens &gt;95%</td>
</tr>
</tbody>
</table>

HIV Treatment

Today’s combination antiretroviral therapy: less toxic, fewer pills, higher genetic barrier to resistance

Goals of HIV care:

- Improve individual health outcomes
- Restore health, prolong life in a manner indistinguishable from uninfected persons
- Lower community viral load and HIV transmission to achieve an “AIDS-free generation”
Buprenorphine and HIV Outcomes

HIV-infected patients treated with office-based bup/nx in the Buprenorphine-HIV Evaluation and Support (BHIVES) national demonstration project:

- Decreased opioid use
- Increased HIV ART use
- Experienced higher quality of HIV care
- Reported better quality of life

Psychiatric Co-Morbidities
Induced vs Independent Disorder

- Distinguish between substance-induced disorders versus independent psychiatric disorders
  - **Substance-induced:** Disorders related to the use of psychoactive substance; typically resolve with sustained abstinence
  - **Independent:** Disorders which arise during times of abstinence; use of psychoactive substances not the etiology
Substance Induced Psychiatric Disorders

- Patient’s history suggests symptoms occur only when he/she is actively using substances
- Symptoms are related to intoxication, withdrawal, or ongoing neurobiologic perturbation from substances
- Onset and/or offset of symptoms are preceded by increases or decreases in substance use
- Goal should be sustained abstinence followed by re-evaluation of symptoms
Substance Independent Psychiatric Disorders

- Earliest psychiatric symptoms often precede onset of substance use disorder
- Patient’s history suggests symptoms occur during periods when not using psychoactive substances
- May also find a family history of the disorder
- Goal of substance use disorder treatment should still be cessation of substance use, but treatment must also address psychiatric symptoms simultaneously
General Treatment Principles

- Patients with opioid use disorder and independent depressive, anxiety, or stress disorders
  - Can respond to medication and/or psychotherapy treatments for depression, anxiety, and PTSD
  - Anxiety disorders and PTSD typically treated with antidepressants
- Generally avoid use of benzodiazepines
  - Risk of misuse
  - Possibility of interactions with buprenorphine
Buprenorphine and Benzodiazepines

- Among 34 reported buprenorphine-associated overdoses in France, 31 also had benzodiazepines.

- Risks of benzodiazepines
  - Tolerance and withdrawal
  - Excess sedation and falls
  - Cognitive impairment
  - Reinforcement/reward/addiction

- Advantages of benzodiazepines
  - Rapid elimination of anxiety symptoms or insomnia when used short term

Buprenorphine and the General Ob/Gyn
Patients

- L.K. 29 y/o G2P0 schoolteacher at 7 weeks with history of chronic pelvic pain presumed to be secondary to endometriosis. On oxycodone extended-release 20 mg bid given to her by pain specialist. Also history of depression on venlafaxine XR 150 mg

- Per patient, she was told to stop oxycodone extended-release and wean off venlafaxine by genetic counselor/MFM consult
W.S.

- 25 y/o G3P2 at 16 weeks referred because of illicit extended release oxycodone use
- Pt started use about 3 years ago because of low-back pain, but then noticed that it helped her deal with life
- Currently using between 30-120 mg a day. Attempted to stop, but after two days had extreme nausea/vomiting/diaphoresis
Substance Use Disorder

- ASAM “primary, chronic, and neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.” The five Cs:
  - Craving
  - Compulsive use
  - Continued use despite harm (consequences)
  - Impaired control over drug use
  - Chronicity (see above)
- Inability to fulfill work and social obligations
- Use in dangerous situations (drunk driving)
- Legal problems
- Interpersonal problems
Definitions

Physical dependence is defined as “a state of adaptation that often includes tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist”

- Tolerance - need for more drug to obtain same effect
- Withdrawal - adverse physical effects secondary to abruptly stopping use
  - Occur in any patient exposed repeatedly to an opiate or stimulant
- Not a marker of SUD if prescribed
So, do these patients have use disorders?

<table>
<thead>
<tr>
<th>Patient #1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>No</td>
</tr>
<tr>
<td>Compulsive use</td>
<td>No</td>
</tr>
<tr>
<td>Continued use despite harm (consequences)</td>
<td>No</td>
</tr>
<tr>
<td>Impaired control over drug use</td>
<td>No</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Yes</td>
</tr>
</tbody>
</table>
So, do these patients have use disorders? (continued)

<table>
<thead>
<tr>
<th>Patient #2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>Yes</td>
</tr>
<tr>
<td>Compulsive use</td>
<td>Yes</td>
</tr>
<tr>
<td>Continued use despite harm (consequences)</td>
<td>Yes</td>
</tr>
<tr>
<td>Impaired control over drug use</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronicity</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Demographics – Prescription Drug Abuse

- Non-medical use of prescription pain medications increased in those ages 18-25 (and younger)
- More people started using prescription pain meds than marijuana or cocaine (NDSUH, 2006)
- More than half women
- Average age 25
- Narcotic analgesics such as hydrocodone, oxycodone, and methadone more likely to cause overdose death than either heroin or cocaine (Maxwell, 2006)
- Prescription opioids were present in 44% of opioid-related deaths in women (Hall, 2009)
Demographics – Chronic Pain

- 15-20% population severe chronic pain at some point
- 15-20% of people with chronic pain have underlying addictive process
- Up to 40% of patients given opioids for chronic pain develop a use disorder
- Most predictive of risk is personal or family history of alcoholism or other addiction (Chou, 2009)
- Women were more likely than men to report use of any prescription opioid (29.8% females vs. 21.1% males, p<0.001) (Green, 2009)
- Women more likely to be given opioids for pain and higher doses (Cicero, 2009)
Pain Management

- Untreated pain can lead to depression, substance abuse, lost productivity
- Opiates for use in chronic pain controversial
- Huge increase in overdose deaths
- Overdose deaths outnumber deaths by MVA
- IR and ER forms are going under federal regulation
- CDC new guidelines
- With increased regulation, seeing increased heroin usage
  - Cheaper and easier to obtain
Opioids and Chronic Pain

- Women more likely to get opioids for
  - Fibromyalgia
  - Headache
  - Osteoarthritis
- Not effective in any of these
- Up-regulate pain receptors, leading to increased pain
- Women at risk for opioid-induced endocrinopathy (Daniell, 2008)
  - Irregular menses
  - Infertility
## Addiction Behaviors Checklist Part 1

<table>
<thead>
<tr>
<th>Addiction behaviors – since last visit</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient used illicit drugs or evidences problem drinking</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>2. Patient has hoarded meds</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>3. Patient used more narcotic than prescribed</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>4. Patient ran out of meds early</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>5. Patient has increased use of narcotics</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>6. Patient used analgesics PRN when prescription is for time limited use</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>7. Patient received narcotics from more than one provider</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>8. Patient bought meds on the streets</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Addiction Behaviors Checklist Part 2

<table>
<thead>
<tr>
<th>Addiction behaviors – within current visit</th>
<th>Y</th>
<th>N</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient appears sedated or confused (e.g., slurred speech, unresponsive)</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>2. Patient expresses worries about addiction</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>3. Patient expressed a strong preference for a specific type of analgesic or a specific route of administration</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>4. Patient expresses concern about future availability of narcotic</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>5. Patient reports worsened relationships with family</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>6. Patient misrepresented analgesic prescription or use</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>7. Patient indicated she or he “needs” or “must have” analgesic meds</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>
Addiction Behaviors Checklist Part 2 (continued)

<table>
<thead>
<tr>
<th>Addiction behaviors – within current visit</th>
<th>Y</th>
<th>N</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Discussion of analgesic meds was the predominant issue of visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Patient exhibited lack of interest in rehab or self-management</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>10. Patient reports minimal/inadequate relief from narcotic analgesic</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>11. Patient indicated difficulty with using medication agreement</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Significant others express concern over patient's use of analgesics</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
</tr>
</tbody>
</table>
Assessment of Addiction

- Med seeking behavior
- Differentiate addiction from “pseudoaddiction”
  - e.g., hoarding meds and asking for refills early could be sign of undertreated pain
  - Some group as part of problematic or aberrant behaviors
- Women less likely to set limits on themselves when dealing with pain and use opioids to help them continue to be productive
- Think about diversion
Methadone and Chronic Pain

- Physicians can prescribe for chronic pain and for patients with use disorders while in the hospital (for another medical indication)
- 213 percent increase in methadone related overdose deaths between 1999-2003 associated with use in pain and not in treatment centers
- Also methadone can prolong QTc and precipitate sudden cardiac death, especially in conjunction with other medications that prolong QTc
Advantages of Buprenorphine

- Don’t have to go to special center for daily dosing
- Less risk of diversion
- NAS less severe than methadone
- Not indicated for treatment of chronic pain, but being used off label.
- Being studied now, anecdotally very effective for certain patients and with chronic pelvic pain which traditionally not well treated with methadone
L.K. (continued)

- Counseled on pain control, weaning, etc.
- Able to wean down to 10 mg every other day, but not able to stop (Pain improved with pregnancy)
- Baby born full term, no NAS
- Breast fed for 1 ½ years
- Pain med needs continued to increase after pregnancy (up to 60 mg bid with hydrocodone/acetaminophen for “breakthrough pain”)
- Amenorrheic
- Hospitalized for severe depression. Admitted to chewing oxycodone extended release for high
As many as 2/3 women with substance use disorders have co-occurring mental health disorders
- Depression
- Anxiety
- PTSD

More likely than men to have depression and anxiety

Up to 80% have history of childhood sexual trauma/IPV

Treatment must account for preconception issues in women of childbearing age
- SSRIs, mood stabilizers, benzodiazepines
Switched to bup/nlxn. Pain better controlled
Counseling/therapy for severe PTSD
SSRI-fluoxetine 100 mg
Quit smoking
Menses return and she gets pregnant (planned and desired)
During pregnancy has hepatitis flare.
  Chronic congenital hepatitis b infection, stopped tenofovir during pregnancy
- Baby born at 37 weeks (cholestasis of pregnancy) by C-section for breech
- Didn’t breast feed (pediatrician didn’t feel comfortable with the tenofovir)
- Baby without NAS
W.S.

- Uneventful induction onto buprenorphine while pregnant
- Delivered at term
- Healthy baby. No NAS
- Still my patient 7 years later 2 relapses
  - Oxycodone x 6 months
  - Meth-brief
- 1 unintended pregnancy-TAB with LNG IUS
- 1 planned uncomplicated pregnancy with term delivery
  - Another LNG IUS
Contraception

- LARC obviously ideal in this population
- Consider immediate postpartum insertion
- Should be addressed frequently
- If not on adequate contraception, should be on folic acid supplementation
  - Preconception opioids and 1st trimester use may be associated with increased risk of neural tube defects
Smoking Cessation

- 51% of people with a history of addiction treatment die of smoking-related causes
- 1.5 X the rate of addiction-related causes
- 63% of all women in addiction treatment smoke cigarettes
- Traditionally not addressed in SA treatment “we’ll work on one thing at a time.”
- Smoking cessation increases abstinence from drug use

SAMHSA 2011, Lemon 2003
SBIRT

- Screening, brief intervention, referral to treatment
- Need universal screening of all women of childbearing age
  - Screening tools-4Ps, NIDA quick screen
  - Conversation, not just the tool
  - Not urine drug monitoring
Pregnancy
Neonatal Abstinence
Breastfeeding
Objectives

At the end of this presentation, participants should be able to:

- Describe the risk/benefit of detoxification from opioids during pregnancy versus medical assisted therapy for the treatment of opioid dependence during pregnancy
- Describe the elements of the multidisciplinary team during pregnancy
- Describe the approach to intrapartum and postpartum pain management during
Options for opioid dependence during pregnancy

- Detoxification
- Methadone
- Buprenorphine
Pregnancy: Initial Evaluation

- Know about specialized treatment services available in the community for pregnant, opioid-dependent patients
  - Referral should be made regardless of the patient’s decision to continue the pregnancy
- Obtain consent to talk to her obstetric provider
Why has detoxification from opioids during pregnancy been long avoided?

Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report

JOSÉ LUIS REMENTERÍA, M.D.
NEMESIO N. NUNAG, M.D.
Bronx, New York

A stillborn infant was born to a drug-addicted mother who had withdrawal symptoms shortly before delivery. Mechanisms are presented to help explain the possible relationship between the maternal withdrawal and the fetal death. Statistics are also presented to show an increased stillborn and neonatal mortality rate in the over-all pregnant drug-addicted population.

There is a fear that any withdrawal will cause fetal harm
Detoxification: Not Best Approach for Maternal Care

- 93 patients
- All offered detoxification
- Gestational age about 20 weeks at entry
- Duration of detoxification: 25 days
- 3 women with fetal demise not counted in statistics: 2 of them failed detox, had no treatment, continued illicit drug use, and presented with IUFD.

42/95 (44%) women were not engaged in treatment, 2 had IUFD

There was no f/u of how the women fared after delivery

Detox can be done: are we treating women only for the benefit of the fetus?

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Variable} & \text{No illicit drug use at delivery, n = 53} & \text{Illicit drug use at delivery, n = 40} & \text{P value} \\
\hline
\text{Max NAS score} & 0 [0, 0] & 8.3 [6.5, 10] & < .001 \\
\text{Infant treated for withdrawal} & 5 (10) & 33 (80) & < .001 \\
\text{Infant hospital duration, d} & 3 [2, 6] & 22 [15, 26] & < .001 \\
\text{Gestational age at delivery} & 39 ± 1.9 & 37.8 ± 2.4 & .008 \\
\hline
\text{Birthweight percentile} & 3065 ± 487 & 2788 ± 516 & .01 \\
\text{<10th} & 7 (13) & 12 (30) & .05 \\
\text{<3rd} & 1 (2) & 2 (5) & .40 \\
\text{5-min Apgar <4} & 0 & 1 (3) & .26 \\
\text{pH <7} & 0 & 0 & NA \\
\text{Neonatal death} & 0 & 0 & NA \\
\hline
\end{array}
\]

Data reported as n (%), mean ± SD, median [First Quartile, Third Quartile].

NA, not applicable; NAS, neonatal abstinence syndrome.

Detox safe. Is it effective?

- Bell et al (2016) reported on 301 patients who underwent detoxification during pregnancy.
- No adverse fetal outcomes (2 IUFDs of those acutely detoxed during first trimester).
- NAS rates 31% (17-70).
- Relapse rates 36% (17-74).
- No control group on MAT (Mother Study-NAS rates 47%).
- Treating a chronic condition with an acute treatment without clear fetal benefit.

### TABLE 1
Demographics, gestational age at the time of detoxification, neonatal intensive care unit admission, and pregnancy outcome of the opiate detox study population

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>108</td>
<td>23</td>
<td>77</td>
<td>95</td>
<td>301</td>
</tr>
<tr>
<td>Mean maternal age, y</td>
<td>26.9 ± 3.7</td>
<td>26.4 ± 3.5</td>
<td>26.6 ± 3.6</td>
<td>27.2 ± 3.9</td>
<td>26.8 ± 3.7</td>
</tr>
<tr>
<td>Maternal age range, y</td>
<td>18–43</td>
<td>17–38</td>
<td>18–39</td>
<td>17–39</td>
<td>17–43</td>
</tr>
<tr>
<td>Maternal age &lt;30 y</td>
<td>82 (76%)</td>
<td>18 (76%)</td>
<td>55 (71%)</td>
<td>67 (72%)</td>
<td>222 (74%)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>94 (87%)</td>
<td>14 (61%)</td>
<td>54 (70%)</td>
<td>73 (78%)</td>
<td>235 (78%)</td>
</tr>
<tr>
<td>White</td>
<td>85 (79%)</td>
<td>22 (96%)</td>
<td>74 (96%)</td>
<td>84 (90%)</td>
<td>265 (88%)</td>
</tr>
<tr>
<td>African-American</td>
<td>22 (20%)</td>
<td>1 (4%)</td>
<td>3 (4%)</td>
<td>8 (8%)</td>
<td>34 (11%)</td>
</tr>
</tbody>
</table>

Gestational age at detoxification and NICU admission

<table>
<thead>
<tr>
<th>Detoxification first trimester, 5–13 wks gestation</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detoxification second trimester, 14–27 wks gestation</td>
<td>10 (9%)</td>
<td>4 (17%)</td>
<td>12 (15%)</td>
<td>2 (2%)</td>
<td>28 (9%)</td>
</tr>
<tr>
<td>Detoxification third trimester, ≥28 wks gestation</td>
<td>33 (31%)</td>
<td>9 (39%)</td>
<td>29 (38%)</td>
<td>54 (59%)</td>
<td>125 (42%)</td>
</tr>
<tr>
<td>Preterm deliveries prior to 37 wks gestation</td>
<td>21 (19%)</td>
<td>3 (13%)</td>
<td>13 (17%)</td>
<td>16 (17%)</td>
<td>53 (17.6%)</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
<td>32 (30%)</td>
<td>5 (22%)</td>
<td>60 (78%)</td>
<td>22 (24%)</td>
<td>119 (40%)</td>
</tr>
</tbody>
</table>

Pregnancy outcome

<table>
<thead>
<tr>
<th>Rate of NAS</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of relapse</td>
<td>22 (23.1%)</td>
<td>4 (17.4%)</td>
<td>57 (74.0%)</td>
<td>21 (22.5%)</td>
<td>107 (36%)</td>
</tr>
</tbody>
</table>

Group 1 consisted of acutely detoxified (unanesthetized patients). Group 2 consisted of inpatient detoxification with intense behavioral health follow-up. Group 3 consisted of inpatient detoxification without intense behavioral health follow-up. Group 4 consisted of inpatient buprenorphine detoxification.

NAS, Neonatal abstinence syndrome; NICU, neonatal intensive care unit.

* One Hispanic in group 1 and one Asian in group 2. Relapse is defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal neonatal neonatal test (and includes all of the patients who had neonatal treated for neonatal abstinence syndrome).

Pregnancy: Benefits of Opioid Agonist Therapy

**Maternal Benefits**
- 70% reduction in overdose related deaths
- Decrease in risk of HIV, HBV, HCV
- Increased engagement in prenatal care and recovery treatment

**Fetal Benefits**
- Reduces fluctuations in maternal opioid levels; reducing fetal stress
- Decrease in intrauterine fetal demise
- Decrease in intrauterine growth restriction
- Decrease in preterm delivery
Opioid Maintenance Therapy

Methadone versus buprenorphine for the treatment of opioid dependence during pregnancy
Pregnancy: Maintenance Therapy Remains the Standard of Care

- Methadone and buprenorphine (both category C) are safe and effective treatment options in pregnancy
- The decision of which therapy to start is complex and should be individualized for each woman
  - Based on available options, patient preference, patients’ previous treatment experiences, disease severity, social supports, and intensity of treatment needed

Jones et al. 2010.
MOTHER Study

Randomized trial of methadone versus buprenorphine

Primary outcome: NAS
- Similar prevalence of treatment for NAS
- Less neonatal abstinence severity and treatment (bup)
- Shorter neonatal LOS (bup)
- Bigger HC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methadone (N=73)</th>
<th>Buprenorphine (N=58)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated for NAS — no. (%)</td>
<td>41 (57)</td>
<td>27 (47)</td>
<td>0.7 (0.2-1.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>NAS peak score</td>
<td>12.8±0.6</td>
<td>11.0±0.6</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Total amount of morphine for NAS — mg</td>
<td>10.4±2.6</td>
<td>11.1±0.7</td>
<td>&lt;0.0091†</td>
<td></td>
</tr>
<tr>
<td>Duration of infant’s hospital stay — days</td>
<td>17.5±1.5</td>
<td>10.0±1.2</td>
<td>&lt;0.0091†</td>
<td></td>
</tr>
<tr>
<td>Infant’s head circumference — cm</td>
<td>33.0±0.3</td>
<td>33.8±0.3</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Secondary neonatal outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment for NAS — days</td>
<td>9.9±1.6</td>
<td>4.1±1.0</td>
<td>&lt;0.003125†</td>
<td></td>
</tr>
<tr>
<td>Weight at birth — g</td>
<td>2878.5±66.3</td>
<td>3093.7±27.6</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Length at birth — cm</td>
<td>47.8±0.5</td>
<td>49.8±0.5</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Preterm, &lt;37 wk — no. (%)</td>
<td>14 (19)</td>
<td>4 (7)</td>
<td>0.3 (0.1-2.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Gestational age at delivery — wk</td>
<td>37.9±0.3</td>
<td>39.1±0.3</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>APGAR score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>8.0±0.2</td>
<td>8.1±0.2</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>9.0±0.1</td>
<td>9.0±0.1</td>
<td>0.69</td>
<td></td>
</tr>
</tbody>
</table>

Jones, NEJM, 2010
MOTHER Study

Secondary outcomes:

- Bigger neonates (bup)
- No difference preterm birth
- Longer gestational age (bup)

Jones, NEJM, 2010
MOTHER Study

Secondary measures: maternal outcomes

- Fewer medical/delivery complications (bup)
- Increased % of women randomized to buprenorphine did not complete the study

Jones, NEJM, 2010
Incidence of infection was low
No significant difference in any outcome by medication: incidence is rare
Notable all 4 PPROM in methadone (NS)
Notable that women on methadone were more likely to present with preterm labor (15% vs. 2%)
Respiratory distress more frequent in neonates of women treated with methadone (19% vs. 5%) (remember average gestational age 37.9 wks for methadone; 39 weeks for buprenorphine)

Take home: women do quite well with either medication

Holbrook, Addiction, 2012
### Summary of outcomes:

<table>
<thead>
<tr>
<th></th>
<th>FAVORS Methadone</th>
<th>EQUIVALENT</th>
<th>FAVORS Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment efficacy</td>
<td><em>better for women that failed treatment in past</em></td>
<td>✗</td>
<td><em>can be considered reasonable first line treatment</em></td>
</tr>
<tr>
<td>Access to treatment</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Requires withdrawal for initiation</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment automatically coordinated</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal medical complications</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td><strong>Neonatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term outcome: data</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>% requiring NAS treatment</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Severity of NAS symptoms</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Duration of NAS treatment</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
</tbody>
</table>
Take Home Message Regarding Methadone and Buprenorphine for the Treatment of Opioid Dependence During Pregnancy

- Methadone or buprenorphine may be used during pregnancy

- It is acceptable care to initiate or maintain women on buprenorphine that meet the criteria and in whom it is the best therapeutic option

- We and many other centers are using buprenorphine routinely for patients presenting for care in whom treatment compliance/access will be improved with buprenorphine

- Buprenorphine may have some benefits over methadone for maternal outcomes; it is certainly not worse compared to methadone
Assemble the Team: It Takes A Village… No Matter the Medication
(And most of us cannot coordinate the village for every patient)

- Pediatrician
- Obstetric provider
- Opioid medication provider
- Substance abuse counselor
- Community based nursing
How to Use Buprenorphine in Pregnancy
Management of Buprenorphine Patient: Newly Pregnant

- For women stable on buprenorphine/naloxone who become pregnant:
  - Current standard of care is to switch to buprenorphine monotherapy at the same dose
  - The combination therapy has been avoided due to the unknown exposure risk of naloxone in pregnancy and concern for misuse causing acute withdrawal and fetal distress
  - Becoming standard of care in some areas because of worry for diversion risk
Considerations

- Do women tolerate buprenorphine?
  - Why did the Mother Study have such a high drop out rate (33% vs. 18%)?

- How much withdrawal can a pregnant woman and her fetus tolerate?
Areas of Concern:

- Why was there a high dropout rate of women randomized to buprenorphine in the MOTHER study? (33% buprenorphine; 18% methadone)

- How much withdrawal can a pregnant woman and her fetus tolerate?

Women that discontinued buprenorphine had higher CINA scores in the first 48 hours after induction.

Holbrook, Drug and Alcohol Dependence, 2013
Fetal Neurologic System Development: Theoretically, fetal withdrawal should not occur until late in gestation

- **1st trimester**
- **2nd trimester**
- **3rd trimester**

- Neuroblast development: 5-25 weeks
- Glial development: 20 weeks through term
- Corticospinal tracts and dendritic development: 24 weeks through childhood
The Cardiovascular Effects of Moderate Withdrawal Are Well-Tolerated in Pregnancy

Meyer, SMFM, 2014
If We’re So Worried About Withdrawal, How Do We Start Bup?

- Ensure moderate withdrawal before initiating treatment and quickly work to get women comfortable with small incremental dosages
  - CINA 10
  - COWS 12

- Induction from methadone to buprenorphine can be associated with higher rates of dissatisfaction with buprenorphine
  - Methadone long half life
  - Higher rates of precipitated withdrawal

- Pregnant women tolerate the cardiovascular effects of moderate withdrawal well

- Need fetal data
  - Third trimester inductions usually done in hospital
Induction Protocol


Stable patient <24 weeks

Outpatient induction scheduled

Patient asked to abstain from opioids 12-24 hrs
COWS scoring: treat as increasing above 10-12
Start with buprenorphine 2-4 mg.
If no precipitated withdrawal in 30 minutes, increase rapidly as needed to obtain symptom control

Usual visit 2-3 hours
Follow-up 1-3 days; adjust as outpatient

Unstable patient > 24 weeks

Admission scheduled: anticipated 24-36 hours

Patient asked to abstain from opioids 12-24 hours
Admission to inpatient /triage. Continuous EFM
COWS scoring: Start with score > 10-12
Start with buprenorphine 2-4 mg.
If no precipitated withdrawal in 30 minutes, increase rapidly as needed to obtain symptom control
Occasionally need anxiolytics/sleep medications

Discharge when reasonably stable
Follow-up 1-3 days; adjust as outpatient
Sample Inpatient Nursing Protocol

- Admit for observation
- Obtain NST upon admission, then bid and prn for COWS > 20
- Regular Diet as tolerated
- COWS score q 2hours until buprenorphine initiated
- Give initial dose buprenorphine 4 mg for COWS > 10
- Observe for 60 minutes. If tolerated and COWS > 6, give additional 4 mg. Repeat COWS q hour and give 4 mg prn COWS > 6. Total first day dose usually 12-16 mg. (occasionally can be higher).
- Day 2 dose is total received day 1 given in am after last dose (or at least 8 hours)
- If switching from methadone or other long-acting opioid, start with 2 mg
- Can give fentanyl or additional bup for precipitated withdrawal
- Rarely need to give Z drugs (zolpidem/eszopiclone/zaleplon) for sleep
  - Hydroxyzine, diphenhydramine work well
Outpatient Follow-up During Pregnancy

Frequent visits allow for frequent feedback/intervention for noncompliance (we have found this really helpful)

- See patient within 1-3 days after initiation of buprenorphine
- Ask about symptoms (checklist) and counseling (confirm)
  (if you do not provide OB care, confirm she is receiving care)
- Provide witnessed urine for drug screen
- Provide prescription for 1 week
  Weekly follow-up visit

For patients that have been quite stable and compliant, we reduce frequency to every 2 weeks
Take Home Message About Buprenorphine Inductions

- Induction can occur in the outpatient setting or overnight stay
- Moderate withdrawal symptoms are well tolerated by pregnant women
- The degree of maternal withdrawal may be important in patient satisfaction with medication
- Dosing in smaller incremental doses may be important in patient satisfaction with medication
- Medication will need to be adjusted frequently for induction and over the course of pregnancy
Withdrawal Symptoms By Visit:
Complaints are frequent; more so when buprenorphine initiated during pregnancy

Key:
- Yellow: Buprenorphine initiated prior to conception (n=18)
- Green: Buprenorphine initiated during pregnancy (n=28)
% Requiring Dose Change by Trimester:
About 2/3 of women on a stable dose prior to pregnancy will need an increase in dose during gestation
Dose Change by Trimester:
The largest dose changes occurred in the second trimester.
Pregnancy change modest in previously stable patients: 4-6 mg.
Fetal Assessment in Women Treated With Methadone or Buprenorphine

Patients:
- MOTHER study
- Maintained on methadone or buprenorphine (blinded)
- BPP/NST 2 hrs prior to a dose; repeated 2 hrs after the dose (peak effect)

<table>
<thead>
<tr>
<th></th>
<th>Predose NST</th>
<th>Postdose NST</th>
<th>Predose BPP</th>
<th>Postdose BPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>No Difference Meth vs bup</td>
<td>More likely non-reactive than pre-dose</td>
<td>No difference*</td>
<td>Both meth and bup: Significant chance reduced movement; Non-sig increased chance of no breathing</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No Difference Meth vs bup</td>
<td>More likely reactive than methadone</td>
<td>*if pre- and post-scores are combined, bup BPP scores higher (8.7± vs 8.2±0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*if pre- and post-scores are combined, bup BPP scores higher (8.7± vs 8.2±0.2)

Interpret antenatal testing cautiously when a few hours after a dose

Salisbury, Addiction, 2012
Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

- Generalized disorder with dysfunction of the autonomic nervous system, GI tract and respiratory system
- Occurs in 60-80% of infants with intrauterine exposure to opioid maintenance therapy
- Onset: majority present within 72 hours after delivery
- Duration: up to 4 weeks (prolonged if exposed intrauterine to more than one substance associated with NAS)
Maintenance Therapy in Pregnancy: Neonatal Abstinence Syndrome (NAS)

- Meta-analysis of 12 studies from 1996-2012: showed buprenorphine exposed neonates (515) compared to methadone exposed (855) had:
  - Shorter mean length of hospital stay (-7.23 days, 95% CI: -10.64, -3.83)
  - In treated neonates, buprenorphine exposed
  - Shorter NAS treatment duration(-8.46 days, 95% CI: -14.48, -2.44)
  - Lower morphine dose (-3.60 mg, 95% CI: -7.26, 0.07)

Brogly et al. 2014.
Maternal Dose and NAS Severity

- No correlation between maternal opioid maintenance therapy dose and the duration or severity of NAS
- Women should be encouraged to report any symptoms of withdrawal through her pregnancy without fear a dose increase will affect her baby’s hospital stay or need for NAS treatment

Opioid Use Disorder and Breastfeeding

- The transfer of methadone and into human milk is minimal and unrelated to maternal doses
- Buprenorphine has poor oral bioavailability and is also compatible with breastfeeding
  - The amount of buprenorphine in human milk is small and unlikely to have negative effects on the infant
- Both are considered Category L3 (probably compatible)

Breastfeeding and NAS

- Benefits of breastfeeding for newborns with NAS
  - 30% decrease the development of NAS
  - 50% decrease in neonatal hospital stay
  - Improved mother-infant bonding
  - Positive reinforcement for maternal recovery

Tobacco Use Contributes to Poor Outcomes of All
Doctor, is there ANY way to reduce the chance my baby will have withdrawal?

Jones HE, Drug and Alcohol Dependence, 2013
Summary of Pregnancy Specific Considerations to Buprenorphine Therapy

- Assess the patient for the best overall treatment plan and recommend medication based on the overall patient needs, not specifically a medication
  - Buprenorphine can be considered first line in patients for whom office based therapy is appropriate
  - Document opioid dependence and increase dose incrementally during induction
- Develop the team approach, obtain the needed consents for free flow of information among the team
  - Medication provider, obstetrics, pediatrics, social work, community based support/nursing
- When antenatal testing is indicated based on standard obstetric indications, try to test patients either early in they day before a dose or in the afternoon hours after a dose
- Encourage smoking cessation/reduction
“Labor is a natural process necessarily attended with more or less violence......it involves exertion which is associated with more or less suffering....”

Barton Hirst MD, System of Obstetrics, 1888
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
- How should post-op pain be managed?

Alford, Annals Int Med 2006
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
  - No: it will create the potential for term withdrawal and relapse, which we have tried to avoid through pregnancy
  - Reasonable to continue whatever medication for opioid dependence to avoid withdrawal

- Does regional analgesia work?

- How should post vaginal delivery pain be managed?

- How should post-op pain be managed?

Alford, Annals Int Med 2006
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
  - Yes
- How should post vaginal delivery pain be managed?
- How should post-op pain be managed?

Alford, Annals Int Med 2006
## Efficacy of Neuraxial Analgesia: Similar

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=36</td>
<td>N=35</td>
</tr>
<tr>
<td>Pain before NA</td>
<td>9 (8, 10)</td>
<td>9 (7.5, 10)</td>
</tr>
<tr>
<td>Pain after NA</td>
<td>1 (0, 3.3)</td>
<td>1.3 (0, 2)</td>
</tr>
<tr>
<td>PCEA settings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (cc/hr)</td>
<td>11.7 ± 1.7</td>
<td>10.6 ± 1.6</td>
</tr>
<tr>
<td>Delay</td>
<td>6.6 ± 1.9</td>
<td>6.1 ± 1.7</td>
</tr>
<tr>
<td>Bolus</td>
<td>8.0 ± 2.8</td>
<td>8.0 ± 2.5</td>
</tr>
<tr>
<td>1 hour max infusion</td>
<td>34.6 ± 1.6</td>
<td>34.0 ± 3.0</td>
</tr>
<tr>
<td>Extra bolus needed during labor</td>
<td>11 (30.6)</td>
<td>4 (11.4)</td>
</tr>
</tbody>
</table>
Efficacy of Neuraxial Analgesia: Similar (Maybe more epidural boluses)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine N=46*</th>
<th>Control N=45*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain before NA</td>
<td>9 (8, 10) N=39</td>
<td>8.8 (8, 10) N=42</td>
<td>0.74</td>
</tr>
<tr>
<td>Pain after NA</td>
<td>2 (0, 3.6) N=34</td>
<td>2 (0, 4) N=41</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**PCEA settings** (Stand Sol: 1/16% bupivacaine + 1 mcg fentanyl/cc)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal (cc/hr)</td>
<td>10.1±0.6 n=46</td>
<td>10.1±0.7 n=42</td>
<td>0.60</td>
</tr>
<tr>
<td>Delay</td>
<td>7.8±2.6 n=46</td>
<td>9.5±1.5 n=42</td>
<td>0.007</td>
</tr>
<tr>
<td>Bolus</td>
<td>6.7±1.6 n=46</td>
<td>7.4±1.3 n=42</td>
<td>0.02</td>
</tr>
<tr>
<td>1 hour max infusion</td>
<td>35.7±1.8 n=46</td>
<td>35.8±1.2 n=41</td>
<td>0.90</td>
</tr>
<tr>
<td>Extra bolus needed</td>
<td>19/46 (30.6)</td>
<td>8/43 (11.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Data omits: one case that had no relief from the epidural and it was felt to be in the wrong space; patient received spinal with good relief; two controls that received epidural but delivered prior to starting PCEA

**not normalized to duration of epidural (yet)
Common Analgesia Questions: Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
  - Similar to other patients: access to short acting opioids
- How should post-op pain be managed?

Alford, Annals Int Med 2006
Postpartum Vaginal Delivery Opioid Use and Pain Score: 24 hrs PP:
Women treated with methadone or buprenorphine have more pain

Meyer, Ob Gyn 2007; Euro J Pain 2010
Common Analgesia Questions:
Women maintained on methadone versus buprenorphine

- Should women stop buprenorphine before delivery to improve pain control?
- Does regional analgesia work?
- How should post vaginal delivery pain be managed?
- How should post-op pain be managed?
  - IV and short acting opioids
  - Consider split dose of maintenance medication
  - PCEA x 24 hrs if severe, intractable pain

Alford, Annals Int Med 2006
Postoperative Cesarean Delivery, Opioid Use and Pain Score: 70% More Opioid Required

Meyer, Ob Gyn 2007; Meyer Euro J Pain 2010
AVOID AGNOIST/ANTAGONISTS:

- Nalbuphine
- Butorphanol
ALERT:
Nalbuphine and butorphanol are partial opioid agonists and can precipitate acute withdrawal in opioid dependent patients

Patient maintained on methadone requested medication for pain
Received nalbuphine 10 mg IV

- Physical Exam
  - Agitated, crying, c/o severe abdominal cramps, muscle cramps - worse in legs, cold w/ shaking chills, tremulous
  - RR subjectively increased no vitals recorded
  - Abd S/NT, fundus soft, ↑BS

- Fetal Tachycardia
Received IV morphine

- Fetal Tachycardia continued x 45min., with subsequent return to baseline
  - No decelerations
Overall Pain Management Approach:
Continue long-acting opioid agonist for treatment of opioid dependence

- Present in labor requesting something for pain
  - Consider either full agonist opioid (NO nalbuphine or butorphanol)
    - Or
    - Offer regional analgesia (expect good response to initial placement; may need additional boluses)

- Vaginal birth
  - Routine postpartum orders with prn opioid analgesics x24 hrs

- Cesarean birth
  - First 24 hrs: anticipate increased needs, consider morphine or hydromorphone PCA; consider PCEA; consider TAP if you anesthesia department does them
  - after 24 hrs: increased potency short acting opioid (hydromorphine) with 50-70% increased dose (4-6 mg po q4-6 hrs); duration of treatment similar
Breastfeeding
Both Buprenorphine and Naloxone Are Compatible With Breastfeeding

Summary of Use during Lactation:
Because of the low levels of buprenorphine in breastmilk, 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. Monitor the infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants. Although unlikely, if the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately. Observe infants for withdrawal signs if breastfeeding is stopped abruptly. The breastfeeding rate among mothers taking buprenorphine for opiate addiction may be lower than in other mothers.

Summary of Use during Lactation:
No information is available on the excretion of naloxone into breastmilk. Because it is not orally bioavailable, it is unlikely to affect the breastfed infant. Studies in nursing mothers have shown that naloxone does not affect lactation hormone levels. If naloxone is required by the mother, it is not a reason to discontinue breastfeeding.

Buprenorphine
CASRN: 52485-79-7

Naloxone
CASRN: 465-65-6
Summary of Use during Lactation:
Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, central nervous system depression and even death. Infant sedation is common and well documented with maternal use of oxycodone. Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of oral oxycodone (and combinations) to a few days. A maximum oxycodone dosage of 30 mg daily is suggested. Oxycodone elimination is decreased in young infants with much inter-individual variability. Monitor the infant closely for drowsiness, adequate weight gain, and developmental milestones, especially in younger, exclusively breastfed infants. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately. Other agents are preferred over oxycodone during breastfeeding.
Assemble the Team: It Takes A Village... No Matter the Medication
(And most of us cannot coordinate the village for every patient)
What About Non-Ob Pain?
Altered Pain Experience

- In experimental pain studies...
  - Patients with active opioid use disorder have less pain tolerance than peers in remission or matched controls
  - Patients with a h/o opioid use disorder have less pain tolerance than siblings without an addiction history
  - Patients on opioid maintenance treatment (i.e. methadone, buprenorphine) have less pain tolerance than matched controls
- Which came first?
  - Opioid use disorder or less pain tolerance?

“Opioid Debt”

- Patients with an opioid use disorder who are physically dependent on Opioid Agonist Treatment (i.e. methadone or buprenorphine) must be maintained on a daily equivalence before ANY analgesic effect is realized with opioids used to treat acute pain.

- Opioid analgesic requirements are often higher due to increased pain sensitivity and opioid cross tolerance.

Acute Pain
Buprenorphine Maintenance Treatment

Theoretical Concern

- May antagonize effects of previously administered opioids
- May block the effects of subsequent administered opioids
- However... Experimental mouse and rat pain models
  - Combination of buprenorphine and full opioid agonists (morphine, oxycodone, hydromorphone, fentanyl) resulted in additive or synergistic effects
  - Receptor occupancy by buprenorphine does not appear to cause impairment of mu-opioid receptor accessibility

Acute Pain

Buprenorphine Maintenance Treatment Options

❖ Continue buprenorphine and titrate short-acting opioid analgesic
❖ D/c buprenorphine, use opioid analgesic, then re-induce
❖ Divide buprenorphine to every 6-8 hours
❖ Use supplemental doses of buprenorphine*
❖ If inpatient,
  • D/c buprenorphine
  • Start methadone 20-40mg (or other long-acting opioid) for opioid debt
  • Use short-acting opioid analgesics
  • Then re-induce w/ buprenorphine when acute pain resolves

Alford, DP; Compton, P; Samet, JH. Ann Intern Med. 2006.
* Book, SW; Myrick, H; Malcolm, R; Strain, EC. Am J Psychiatry. 2007.
Chronic Pain

Buprenorphine Maintenance Treatment

- Systematic review
- 10 trials involving 1,190 patients
- Due to heterogeneity of studies, pooling results and meta-analysis not possible
- All studies reported effectiveness in treating chronic pain
- Majority of studies were observational and low quality
- Current evidence insufficient to determine effectiveness of SL buprenorphine for treatment of chronic pain
- Expert opinion supports the use of buprenorphine for chronic pain in patients diagnosed with an opioid use disorder
- Needs to be dosed q6-8 hours. May not have a ceiling effect for pain

Overdose Prevention

- Naloxone should be prescribed to everyone with an opioid use disorder
- Pregnant women should receive naloxone in cases of overdose to prevent death to mother and fetus
- Available formulations
- Families also need to have it available
Providers’ Clinical Support System
For Medication Assisted Treatment

What We Do
We are a national training and mentoring project developed in response to the prescription opioid misuse epidemic and the availability of newer pharmacotherapies to address opioid use disorder. The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

View Modules
The foundation for provider education on topics related to medication-assisted treatment for opioid use disorder.
Start Training

Find a Mentor
The mentor program provides individualized support and mentoring for providers treating opioid use disorder.
Connect Now

Watch Webinars
Webinars provide expanded education targeted at clinicians engaged in the treatment of opioid-dependent patients.
Watch Now

ASAM American Society of Addiction Medicine

Treatment of Opioid Use Disorder Course
Includes waiver qualifying requirements
Some women are surprised to learn they got pregnant while using heroin, oxycodone, or other pain medications. These medications can increase the risk of complications during pregnancy. There are no known opioid medications that are safe for use during pregnancy, and it is important for women to seek treatment for opioid use disorder before or during pregnancy. If you are pregnant and are using opioids, you should talk to your healthcare provider about the risks and benefits of continued use. It is recommended that all women who are pregnant or planning to become pregnant seek medical care from a qualified obstetrician-gynecologist to ensure the best possible outcome for both mother and baby.

HOW CAN I GET STARTED ON METHADONE OR BUPRENORPHINE?

- Contact a local treatment center or substance use disorder program to discuss your options.
- Many providers offer a free or low-cost clinic for those who qualify.
- You can call 1-800-HELP-NOW (1-800-435-7669) to find a treatment center near you.

WHAT IS THE BEST DOSAGE OF METHADONE OR BUPRENORPHINE DURING PREGNANCY?

The dose of methadone or buprenorphine during pregnancy should be reduced by 50% to 75% of the non-pregnant dose. This allows for a lower risk of withdrawal in the newborn. For the first 2-3 months of pregnancy, the dose should be decreased by 50%. After that, the dose should be decreased by 25% every month until delivery. For the last 6-8 weeks of pregnancy, the dose should be decreased by 12.5% every week. It is important to work closely with your healthcare provider to ensure that you are receiving the appropriate dosage for your individual needs.

If you are pregnant and using opioids, it is important to seek medical care from a qualified obstetrician-gynecologist as soon as possible. They can help you understand your options and develop a plan to safely taper off opioids during pregnancy. It is important to discuss with your healthcare provider the risks and benefits of continued use to ensure the best possible outcome for both mother and baby.
CHILDBIRTH, BREASTFEEDING AND INFANT CARE: Methadone and Buprenorphine

HOW SHOULD I PREPARE FOR DELIVERY?
- Choosing a doctor and hospital with experience in methadone and buprenorphine during labor and delivery can be helpful.
- Select a doctor for your baby (a pediatrician or family physician) and meet before delivery to talk about the care of your baby.
- Find out whether you can take the nursery before your baby is born to learn about how the nursery cares for opioid-exposed infants.

WHAT ABOUT PAIN RELIEF DURING AND AFTER DELIVERY?
- Your usual daily methadone or buprenorphine dose will not treat pain.
- Discuss pain control for childbirth and labor and delivery with your physician during prenatal care.
- Meet with the anesthesiologist to discuss your labor and delivery plan. This meeting can happen before labor or early in labor.
- If you are having a planned cesarean delivery or have one after labor, discuss postoperative pain.
- The doctors on Labor and Delivery MUST know that you are taking methadone or buprenorphine so that you are not given labor pain medications such as Stadol and Nubain which can cause withdrawal in women taking methadone or buprenorphine.

ARE YOU PREGNANT, TAKING METHADONE OR BUPRENORPHINE, AND WANT TO KNOW HOW THIS MAY AFFECT YOUR DELIVERY, ABILITY TO BREASTFEED, OR YOUR NEWBORN?
- If you are pregnant, taking methadone or buprenorphine, and want to know how this may affect your delivery, ability to breastfeed, or your newborn?
- Or are you a pregnant woman using heroin or prescription opioids and considering treatment with methadone or buprenorphine?

HOW DOES OPION WITHDRAWAL AFFECT THE BABY AFTER DELIVERY?
- After delivery, the baby no longer receives nutrients and medications such as buprenorphine and methadone from the mother’s bloodstream. Your baby may develop withdrawal—called Neonatal Abstinence Syndrome (NAS).
- Not all babies born to mothers on methadone or buprenorphine develop NAS.
- Each baby shows withdrawal differently. The following are some of the common symptoms in opioid-exposed babies:
- Tremors or shakes
- Crying
- Poor feeding/hunger
- Miosis
- Shivering
- Convulsions
- Irritability
- Fussiness
- Grimacing
- Stuffy nose
- Frequent vomiting
- Changes in sleep patterns
- Fasting
- Diarrhea
- Fever
- Leukocyte count
- Babies with NAS may have one or several symptoms.
- These signs may last from birth to 7 days after delivery and can last days, weeks, or months.
- Your baby may need medication to treat these symptoms and make the baby feel better. The baby's dose will then be decreased over time, until the symptoms have stopped.
- Your baby may be watched for four or five days in the hospital to see if medication will be needed.
- If a baby has NAS, it does not mean that he or she will have long-term problems.

CAN I BREASTFEED IF I AM TAKING BUPRENORPHINE OR METHADONE?
- Breastfeeding is usually encouraged for women who are taking methadone or buprenorphine, except in some cases.
- Breastfeeding is not safe for women who are taking certain medications that are not safe in breastfeeding, or who are smoking during pregnancy.
- Only very small amounts of methadone and buprenorphine get into the baby's blood and may help lessen the symptoms of NAS.
- If you are breastfeeding, please talk to your doctor and other health care providers about the best protection for you and your baby.
- A breastfeeding support worker may come to your home to teach how to breastfeed your baby.
- If you are breastfeeding, your baby may be given medication to help with withdrawal symptoms.
- Your baby may have difficulty breathing, feeding, or sleeping.
- Your baby may need medication to treat these symptoms, and make the baby feel better.
- The baby's dose of medication will then be decreased over time, until the symptoms have stopped.
- Your baby may be watched for four or five days in the hospital to see if medication will be needed.
- If a baby has NAS, it does not mean that he or she will have long-term problems.

WHAT ABOUT CHILD PROTECTIVE SERVICES?
- Many babies and newborns get tested for drugs and alcohol at delivery—this might include methadone and buprenorphine.
- Having a positive drug test even if it is for prescription medications may mean that social workers or a child protection agency will want to talk to you, and your family.
- A child welfare worker may come to your home to see how safe the environment is for your baby.
- If you have concerns about your baby, please talk to your doctor and other health care providers about the best protection for you and your baby.

HOW WILL HAVING A NEWBORN AFFECT MY RECOVERY?
- The weeks and months after the baby is born can be a stressful time for women in recovery. Be sure to continue counseling, and use parenting support programs.
- Do not make a decision to stop your opioid medication too quickly or too soon because this increases the risk of relapse.
- It is important to discuss decisions about your medication with your doctors and your counselor. For further information, please see "Breastfeeding and Pregnancy Use Methadone and Buprenorphine."
Billing/Coding

- Pregnant women can bill E:M code in addition to global Ob. Usually time-based.
- Screening, brief intervention, referral to treatment has separate E:M code:
  - 99408 and 99409
  - H0049 and H0050-Medicare
- If not pregnant, again use E:M coding.
Questions?
Completing the Waiver Paperwork
BUPRENORPHINE Waiver Notification Form

Entering a 30 Patient Notification
Submitting a 30 patient Notification form on line

Buprenorphine Waiver Notification

Before you begin
Before starting this application, please make sure you have
- Your DEA Number
- Your State Medical License Number
- Your Training Certificate Information

Do you work for the US military, Veterans Administration, or Indian Health Service?

Answer the question yes or no and click the Next button.
Check your eligibility

• Use the drop down menu to select your licensing state.
• Enter your medical license number, letters and numbers only. No spaces or dashes.
• Enter your DEA number, letters and numbers only.
• Click the Submit button.
The system will indicate the number of patients you are eligible to submit a Notification for. Click the Next button.

The state, medical license and DEA number will be pre-populated.
Complete Notification Form

1A. Enter your name and suffix. (M.D. or D.O.)
1B. Medical license number will be pre-populated
1C. License state will be pre-populated
1D. DEA number will be pre-populated
2. Address – if you are plan to store buprenorphine on site you will need to provide the address you are listed under with DEA. Otherwise you may provide an address in your licensing state. Do not enter a P.O. Box as your street address.

3. Enter phone number

4. Enter fax number

5. Enter email address, twice. Please provide an email address the regularly access. All correspondence form SAMHSA will be via email.
6. Purpose of Notification
the New box will be pre-checked

7. Check the box, that you will only use approved Schedule III, IV, & V medications
8. Certification of Qualifying Criteria
Check the appropriate box if you have a sub-specialty in Addiction medicine or psychiatry. Check the appropriate box for the 8 hour training course you completed. Enter the date the training was completed. Enter the city where the training was completed. If you have complete an on-line course type “web” for your city. The state will be pre-populated but you may change it if it does not correspond with where you complete on site training.
9. Certification of Capacity
Check box – must certify that you will refer patients for counseling.

10. Certification of Maximum Patient Load – button is pre-populated

11. Consent to Release Contact Information – click the “consent” or “do not consent” button

12. Check the box which states that you have not knowingly given false information.
Type your name in the box as your signature.
Type in your DEA number matching the one you entered initially.
Click the Submit button.
When the Notification is submitted successfully you will receive a confirmation. If it has not, an error message will indicate what needs to be corrected.
Thank You

Questions? Email education@ASAM.org or call 301.656.3920