Buprenorphine in Pregnancy: The Basics

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Mitigating Potential Bias

- We have no financial relationships to disclose
Learning Objectives

At the end of the session, the participants will be able to:

1. Identify the risks associated with untreated opioid dependence in pregnancy

2. Recognize the benefits and disadvantages of each of the three major opioid agonist treatments (methadone, buprenorphine, morphine)

3. Review evidence from the MOTHER study supporting the use of buprenorphine in pregnancy

4. Develop an approach to buprenorphine initiation, titration and maintenance

5. Review the evidence for breast-feeding on buprenorphine
Opioid Maintenance Therapy in Pregnancy: Unmet Needs
Opioids: The rising need for treatment in diverse environments

- Canada has highest per capita consumption of oxycodone in the world (2011)
- Prescription opioid use rising, but heroin still most widely cited opioid used in pregnancy
- Rural & remote: communities at risk of lack of providers:
  - Stats Can: Population < 10,000 with less than 30% population traveling to a city for work
  - CMA: based on call requirements of physicians, access to specialists
  - Issue: how many of people in the communities have access to a methadone physician and/or pharmacy

Jumah et al, 2014
Untreated Opioid Addiction: Maternal Complications

- Six-fold increase in maternal obstetric complications:
  - Preeclampsia
  - Third trimester bleeding
  - Premature labour
  - Spontaneous miscarriage

- Cause: recurrent (often daily) opioid withdrawal causes uterine irritability

- Other maternal issues:
  - Maternal-neonatal transmission of HIV and Hepatitis C
  - Poor attendance at prenatal care
  - Poor nutrition
  - Concurrent use of other drugs: tobacco, cannabis, cocaine, alcohol

Wong et al, 2011; Ordean et al, 2008
Untreated opioid addiction: Neonatal Complications

- Neonatal mortality due to low birth weight and prematurity
- 74-fold increase in sudden infant death syndrome (Minozzi et al, 2009)
- Neonatal abstinence syndrome occurs both with AND without treatment of opioid dependence
- However, NAS without maternal/parental preparation has significant impact on infant, mother & extended family
Opioid Agonist Therapy

- Opioid agonists used in pregnancy: buprenorphine, methadone or morphine (long-acting)

- Dose titrated to relieve withdrawal symptoms and cravings for 24 hours

- Continue treatment throughout pregnancy and at least first six months post-natal

- Methadone providers can play an important role in expanding treatment of opioid use disorders in pregnancy through education and support for buprenorphine given the expansion of funding models and support for community-based prescribing
Methadone: The gold-standard?

- Significant areas of Ontario where methadone prescriber or pharmacy not readily available

- Changing landscape in Ontario based on ODB & NIHB changes
  - Buprenorphine-naloxone on ODB formulary as of Fall 2012 (LU Code required)
  - Health Canada approval for buprenorphine monopromid - 2 weeks
  - Buprenorphine-naloxone available on NIHB as of Sept 2014

- No special license required for buprenorphine
  - Although recommended to take Opioid Prescribing Course or other CME

- In some aboriginal communities methadone is not allowed on reserve due to safety concerns
Opioid Agonist Therapy: methadone, buprenorphine or morphine?
Three drugs are similar:

- All three drugs are opioids with slow onset, long duration of action
- They relieve withdrawal, cravings without sedation or euphoria
- Illicit drug use can be monitored with urine drug screens
- Numerous controlled trials: OMT is by far the most effective Rx for opioid addiction in non-pregnant patients
Methadone:

**Advantages:**
- >40 year hx of documented safety and efficacy in pregnancy
- Decreases erratic maternal opioids and fetal exposure to repeated withdrawal episodes
- Decreases illicit drug use (therefore fetal exposure)
- Decreased risks of fetal exposure to: HIV, hepatitis and STIs (Kaltenbach, 1998)

**Disadvantages:**
- MDs need special license from CPSO
- Need pharmacy open 7 days per week and not all pharmacies dispense
- Strict policies wrt to dosing and take-home dose
- High risk of overdose (especially during initiation phase)**
- Positive relationship between methadone and NAS severity (as compared with BUP)
  - Although increasing dose does not increase risk of NAS
Slow-Release Morphine:

Advantages:
- Readily available
- No special license for MDs
- No special training for pharmacies
- Less stigma (in pregnancy)

Disadvantages:
- Need a once-daily dosing so only Kadian® suitable
  - Will likely need twice daily dosing (split dosing by the end of pregnancy)
  - Smallest dose available: 10 mg
- **CPSO recommendations:** Can be prescribed for up to 6 months
  - Only to be used if buprenorphine/methadone not available (CPSO Policy statement #10-01, March/April 2002)
- Urine drug screens less reliable for illicit substance use
Buprenorphine

Advantages:

- Partial agonist at mu receptor
  - May contribute to less severe NAS/?decreased NAS rates

- Lower overdose risk

- More leniency in terms of take-home doses

- No special license required

- Available in rural/remote/underserviced areas subject to available resources for induction

Disadvantages:

- Buprenorphine-naloxone) is not recommended in pregnancy
  - Naloxone: fetal effects unknown, category B drug with no reported tetragenicity in animals/humans
  - One small retrospective study of 10 patients (Lund, 2013)

- Buprenorphine is only available through the Health Canada compassionate release program
  - Can take up to two weeks or longer to get the drug

- MD must dispense Subutex®

- New initiation: must be in moderate withdrawal
  - May not be able to titrate fast enough to avoid discontinuation
Effectiveness of M, Morph, Bup

- Cochrane review of RCTs with pregnant opioid-addicted women
  - 4 trials methadone vs buprenorphine, one trial methadone vs morphine

- All three drugs similar in:
  - Maternal reduction of opioid use and treatment retention
  - Decreased prematurity and increased birth weights

- New (2014) WHO guidelines indicate can use buprenorphine OR methadone in pregnancy
  - Given the same weight in the guidelines


Slide adapted from: Jones, 2011
Buprenorphine: The evidence
MOTHER Study: Methadone vs. Bup in pregnancy

Adapted from: Jones, 2011

Double blind / double dummy
**Flexible dosing
MOTHER STUDY: neonatal outcomes

- Compared with methadone-exposed neonates, buprenorphine-exposed neonates
  - Required 89% less morphine to treat NAS
  - Spent 43% less time in the hospital
  - Spent 58% less time in the hospital being medicated for NAS

- Both medications in the context of comprehensive care produced similar maternal treatment and delivery outcomes

Adapted from: Jones, 2011
MOTHER STUDY: other outcomes

Adapted from: Jones, 2011

There was a significant difference between medications in the mean time to initiation of morphine treatment for those neonates treated for NAS.
Buprenorphine: The initiation
Buprenorphine: Initial Documentation

- UDS: documenting opioids present = dependence
  - No methadone, fentanyl (to help mitigate risk of precipitated withdrawal)
  - If do not have urine drug screen facilities available, ensure careful counseling of patient

- Criteria for dependence (severe opioid use disorder)

- If possible, document LMP or EDC if known

- Document presence of any pv bleeding
  - Will want to know to monitor impact of withdrawal on stability of pregnancy

- Document presence of nausea and vomiting
  - May want to consider pre-treatment with anti-emetics 30-60 min prior to buprenorphine
Buprenorphine: Initiation

- Arrive clinic, 10-12 hours after last use of short-acting opioids
- COWS on arrival and q1hour until score > 10
- COWS > 10; give 4 mg SL buprenorphine
- Monitor x 60 min – no worsening symptoms; give an additional 4 mg
- Monitor further 120 min – if ongoing w/d give an additional 4 mg for total of 12 mg on day 1
- In communities where daily dosing may be part of treatment programming, have the patient return in AM for total day 1 dose OR
  - Send home with script to take following AM for total day 1 dose
Buprenorphine: Initiation

- What if > 12h since last use; COW < 10
- If cows > 6; **give 2 mg test dose**
- **If no worsening symptoms of w/d over next 60 min; give 4 mg dose**
- Monitor additional 120 min, if additional w/d; **give additional 4 mg** (otherwise hold)
- **Follow-up next day to discuss dosing and/or ongoing withdrawal**
  - Best to do early in the day so that you can provide additional doses, if needed
  - *Often first time patients are seen with clear sensorium*
Buprenorphine: Other treatment

- Advantages of observed dosing in opioid agonist therapy:
  - Changing of behavioural patterns including structure
  - Development of new behaviours (attendance at clinic/pharmacy)
  - Increases contact with health care providers and issues with dosing can be managed earlier

- Need to be sensitive to community concerns especially in rural and remote communities where daily dosing may be part of treatment programming
  - Guidelines are not completely regimented with respect to carries and observed doses; community norms are important to support

- Individual and group addiction counseling

- Contingency management for acquisition of carries
Buprenorphine: Vomiting

- What if the patient vomits after taking buprenorphine? Should the dose be replaced?

- Buprenorphine expected to be absorbed SL within 2-7 mins

- If patient experiencing ++ NVP, can break/crush SL tab during observation to increase surface area for absorption

- Can pre-treat 30-60 mins prior to dose with anti-emetic

- If dose dissolved prior to N/V then dose does not need to be replaced

- If concerned about w/d, unclear if dose dissolved, have pt return later that day to clinic to observe for clinical signs of withdrawal
# Medications for NVP: ODB Coverage

<table>
<thead>
<tr>
<th>Agent</th>
<th>ODB Coverage</th>
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<tbody>
<tr>
<td>Doxylamine + B6 (Diclectin®)</td>
<td>YES*</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>NO</td>
</tr>
<tr>
<td>Promethazine</td>
<td>NO</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>YES</td>
</tr>
<tr>
<td>Promethazine</td>
<td>NO</td>
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<tr>
<td>Metoclopramide</td>
<td>YES</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>NO**</td>
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</tbody>
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* Diclectin considered first-line by SOGC (NVP Guidelines)
** 4mg tab x 30 days: > $650
Buprenorphine: Dosing in Pregnancy

- Greater plasma volume
- Increased renal blood flow
- Induction CYP3A
  - Possible contribution of CYP3A7 from fetus
- Increased tissue binding
- T1 to T2: Dose increases
- T2 to T3: Split dosing (+ inc)

**SUPPORT THE DOSE THAT PREVENTS WITHDRAWAL AND CRAVINGS**

Pond, 1985; Swift, 1989; Jarvis, 1999; Wolff, 2004; Selligman, 2010
Adapted from: Jones, 2011
When women become pregnant on buprenorphine-naloxone

- Literature supports that harm unlikely if fetus is exposed to naloxone (category B)
- Change to buprenorphine alone can take time (2 weeks +) so it is important to maintain ongoing treatment
  - Continue with same dose of buprenorphine-naloxone with appropriate increases
- Women should have an informed consent discussion of the benefits of treatment versus cessation of treatment
- Women should be counseled at buprenorphine initiation (outside of pregnancy) that current guidelines recommend the switch to the monoprodut
- Particularly in light of the fact that a switch to long-acting opiates may improve fertility (and promote pregnancy)
Buprenorphine: Breast-feeding?

- Few studies/info re: buprenorphine and BF’ing
- Benefits of breastfeeding may outweigh the risks of not breastfeeding
- **What we do know:** Low levels in breast milk, poor bioavailability, low concentration in newborn serum/urine
  
  (ACOG Committee Opinion 2012; US Department of Health and Human Services 2004; Jones 2012)

- Little info re: naloxone and BF’ing but typically can only get Subutex® x 6 weeks post partum

- Naloxone has poor oral bioavailability so likely little transferred to breast milk
  
  - If naloxone is required by the mother, it is NOT a reason to discontinue breastfeeding (LACTMED)
Neonatal Abstinence Syndrome (NAS): Ontario Stats

15-fold increase in NAS numbers in 20 year period

Final 5 years: 927 deliveries of infants with neonatal abstinence syndrome in Ontario to mothers who were public drug plan beneficiaries

What should your patients expect re: NAS?

- Start discussing NAS early (suggest starting at 24 weeks – viability) and ongoing throughout pregnancy

- Recommend antenatal consultation with paediatrics in third trimester (28-32 weeks) re: NAS

- Reinforce NAS is treatable condition (morphine) and babe is very comfortable once treated

- Woman and her family play an important role in soothing child/kangaroo care – woman can act as an advocate for her child

- Children exposed to methadone or buprenorphine as part of an opioid maintenance treatment program do not show any long-term developmental issues associated with in utero exposure to methadone/buprenorphine
What should your patients expect re: NAS?

- Travel back-and-forth daily to hospital if baby requires treatment
  - 3 week average stay in nursery (Turner, in review)

- 3 decades of research shows an inconsistent relationship between maternal methadone dose and NAS severity
  - Bottom line: Mum should take the dose that keeps them stable (Cleary et al., 2010; Selligman, 2010)
  - Almost no data on buprenorphine dose and NAS severity

- Longer hospital stay post-delivery for NAS monitoring
  - NAS signs develop in 55-90% newborns; treatment in approx 70%
  - NAS develops/peaks in METHADONE exposed newborns: 72h-120h; Longer peak in BUPRENORPHINE (should be monitored for a minimum of 7 days)
  - Treatment involves treatment of morphine (first-line)
Thanks to:
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What do you need to know about detox/tapering in pregnancy?
Tapering: The benefits

- Tapering (and or detox) during pregnancy will prevent complications of acute withdrawal (i.e. premature labour; spontaneous abortion)

- Tapering will also minimize or prevent Neonatal Abstinence Syndrome (NAS)

- Taper when:
  - Motivated and ready
  - Not using and no cravings
  - ?short-period of addiction
  - Has made lifestyle changes

- How many pregnant patients in your practice would meet these criteria?

- What if there is no other way to engage in treatment?
Tapering: How to do it?

- 5-10% per week of total dose – assuming is on prescription opioids or has been transitioned to long-acting opioids (methadone/bup)
  - Methadone 100 mg – initially decrease by 10mg (to 90 mg), following week decrease by 9 mg (to 81mg), etc

- Stop taper if any adverse outcomes such as relapse to drug use, increased cravings or intolerable withdrawal symptoms (i.e. abdominal cramping)

- Suggest only consider after transition to methadone or buprenorphine
  - This allows for continuation in OMT if taper is not going well
  - As well, monitoring with UDS is part of the treatment paradigm

- Initiation may be considered in hospital (more about this later) but suggest slow taper as outpatient
Tapering: The evidence – non-pregnant patients

- 4000 methadone tapers in BC over 10 year period (Nosyk, 2012)

- **Success rate 13% at 18 months post-taper**
  - No Rx re-entry
  - No opioid hospitalization
  - No death in the 18 months following taper

- Successful tapers:
  - Slow (OR 6.5 for > 52 weeks vs < 12 weeks)
  - Taper interspersed with stabilization periods (OR 2)

- **Difficult to replicate in pregnancy given the long timeline required**
Tapering: The evidence – pregnant patients

- Compared 5 scenarios (Jones, 2008):
  - 3day meth taper
  - 3day meth taper + MMT
  - 7day meth taper
  - 7day meth taper + MMT
  - MMT

- All MMT patients did better in terms of:
  - Fewer + UDS at delivery
  - Days in treatment
  - Attended more OB appts

- MMT from outset had best outcomes
Tapering: The disadvantages

- Sub-acute withdrawal often lasts for 12+ weeks after taper complete
  - Insomnia
  - Intense cravings
  - Depression and suicidal ideation

- Also patient has same drug-using environment, same ways of coping with stress

- A short period of abstinence puts the woman at risk for overdose if she relapses
  - Fatal and non-fatal overdose rate higher in detoxed patients than in patients who keep using

- Naloxone generally contraindicated in pregnancy
What’s an addiction provider to say?

- Suggest transition to methadone or buprenorphine and consider tapering if on a stable dose

- We know that relapse is ++ common, unlikely to attend OB appts, likely to have positive UDS at delivery if the patient “detoxes” or tapers

- Most guidelines suggest maintenance in pregnancy and for at least six months post-delivery

- Allows time for mother-baby attachment; favourably viewed by child-protection agencies

- Gets mother through stress of pregnancy and looking after small infant and the multiple risk factors for relapse
  - Decreased sleep
  - Increase in mood changes
  - Change in relationships
  - Isolation