PainWeek

To Dream The Impossible Dream: Acute Pain Management for Patients on Buprenorphine

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Disclosure

- Nothing to disclose

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Learning Objectives

- Describe how the pharmacokinetic properties of buprenorphine affect both pain and substance use disorder (SUD) treatments.
- Differentiate buprenorphine used for treatment of pain from its role in SUD.
- Recommend strategies for the treatment of acute pain in patients on buprenorphine therapy.

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Scenario 1

- HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, and is successfully managed on buprenorphine/naloxone (BUP/NALx) for 5 years.
- The Team wants recommendations on how to treat her pain post-operatively as well as what to do about the BUP/NALx?

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Scenario 2

- HG is in a car accident and is admitted with a broken femur and a few broken ribs. She has a history of opioid addiction and remains successfully managed with buprenorphine/naloxone for substance use disorder (SUD).
- She is in severe pain and the team wants to know how to manage her pain and what to do with her BUP/NALx?

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Scenario 3

- HG has remained cancer free, and remains maintained on her dose of BUP/NALx. Her biological clock is ticking; she is happy to report that she is now pregnant. She is concerned that he BUP/NALx will be harmful for her baby.
- How do we manage her pain during and after delivery?

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Buprenorphine Pharmacology

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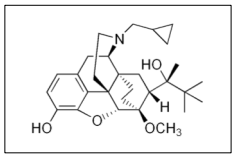
Buprenorphine

- FDA approved for treatment of substance abuse and moderate to severe pain
- Substance abuse: SL
- Pain: buccal film, transdermal patches, parenteral



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Buprenorphine PK

- Partial agonist - mu receptor; antagonist- kappa receptor
- Has high affinity and binding capacity for the mu receptor, but low intrinsic activity
- T½ = 24-42 hours, IV = ~3.5 hours
- Slow dissociation from receptors and extended activity
- Lipophilic, not eliminated by the p-glycoprotein efflux pump
- CYP3A4 primarily – active metabolite norbuprenorphine

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Pharmacokinetic Parameters

PK Parameter	Buprenorphine (SL & Top)
Protein Binding	96%
Bioavailability	SL: 29%; Top:~ 15%
Half-life Elimination	SL:~37 hrs; Top: ~26 hrs
Onset of Action	10-30 min
Duration of Action	6 hrs
Time to Peak	SL: 30-60min
Time to Peak Effect	N/A
Decreased Hepatic Function	Mild-Mod dysfunction: adjust dose/monitor
Decreased Renal Function	N/A
Geriatric	Monitor

Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2004. (Treatment Improvement Protocol (TIP) Series, No. 40.) 2 Pharmacology.Available from:http://www.ncbi.nlm.nih.gov/books/NBK64236; Lexicomp On Line 2014; Epocrates on Line 2014; American Hospital Formulary Service

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Buprenorphine MOA

- Potent analgesic – can produce effective analgesia with only 5-10% of mu receptors occupied
- Short half-life (IV); long duration of action due to high receptor affinity
  - Half-life and receptor affinity determine the duration of action of a substance
  - Buprenorphine will continue to occupy receptors for 24 to 72 hours, depending on the administered dose

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Buprenorphine (BUP) for Pain and Substance Use Disorder (SUD)

- Effective for pain control in patients with/without substance abuse history
- Associated with reductions in pain when transitioned from high dose opioids
  - –BUP may exhibit a hypoalgesic effect
- Adverse effects seen mostly with either high dose (>300 mg) or low dose (<20 mg) morphine equivalents
  - –Patients more likely to stop treatment
  - –Dosing flexibility needed with treatment of both chronic pain and abuse
- Lower doses generally used for pain vs. SUD dosing
  - –Transdermal patch OK to continue perioperatively

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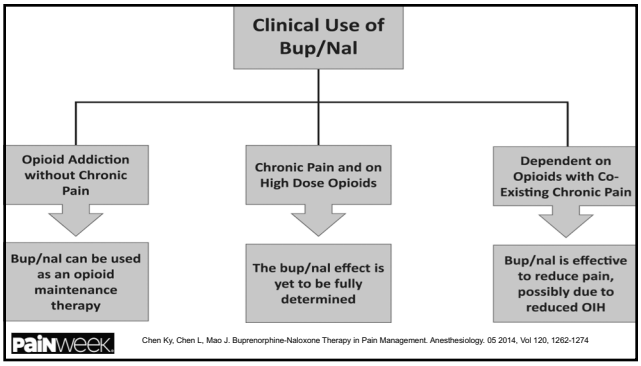

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Chen Ky, Chen L, Mao J. Buprenorphine-Naloxone Therapy in Pain Management. Anesthesiology. 05 2014, Vol 120, 1262-1274

Misconceptions

1. Maintenance opioid agonist provides analgesia
2. Use of opioids for analgesia may result in relapse
3. Additive effects of opioid analgesics and maintenance opioid agonist will result in respiratory depression and CNS depression
4. Reports of uncontrolled pain may be manipulation/drug-seeking behavior

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Alford DP, et al. *Ann Intern Med* 2006;144:127-134.

Dosing for Pain

- Sublingual
  - –Buprenorphine (with/without) naloxone 4–16mg in divided doses q 6-8 hours
  - –Less respiratory depression than w/ full mu agonist opioid
  - –Do not need "X" waiver to prescribe
  - –Not FDA indication; possible insurance restrictions
- Buccal film
  - –Dosing dependent on prior exposure to opioid therapy
  - –<30 mg Oral Morphine Equivalents (OME): 75 mcg daily or q12
  - –30-89 OME: 150 mcg q12h
  - –90-160 OME: 300 mcg q12
  - –Titrate by 150 mcg/dose as indicated

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Pain Med. 2014 Sep 12. doi: 10.1111/pme.12520. [Epub ahead of print; Pain Physician. 2012 Jul;15(3 Suppl):ES59-66; Am J Ther. 2005 Sep-Oct;12(5):379-84; J Addict Dis. 2013 January ; 32(1): 68–78. doi:10.1080/10550887.2012.759872.; Pain Med. 2014 Jul;15(7):1171-8. doi: 10.1111/pme.12386. Epub 2014 Jul 4

Dosing

- Topical: Patch
  - Titration Interval: min = 72 hours; q 7 days
  - Opioid-naïve patients: Initial - 5mcg/hour applied q 7 days
  - Opioid Tolerant:
    - Max. dose= 20 mcg/hour applied q 7 days
    - May not provide adequate analgesia, consider use of alternate analgesic
    - Not indicated in patients on >80 mg day oral morphine equivalents

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
Recommended BUTRANS Starting Dose	5 mcg/hour	10 mcg/hour

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Pharmacokinetic Parameters

PK Parameter	Buprenorphine (SL & Top)
Metabolism	CYP 3A4
Drug Interactions: Avoid Concomitant Use	Azelastine, MAOI, Orphenadrine, Paraldehyde, Thalidomide
Drug Interactions: Metabolism	Substrate of CYP 3A4 (major); weakly inhibits CYP 1A2; CYP 2A6; CYP 2C19; CYP 2D6

Lexicomp On Line 2018, American Hospital Formulary Service 2018

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Drug-Drug Interactions

Increased opioid effect

- Alcohol
- Antiretroviral
  - Atazanavir
  - Indinavir
  - Nevirapine
  - Ritonavir
  - Saquinivir
- Benzodiazepines
- Fluvoxamine
- Ketoconazole

Decreased opioid effect

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin

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ACUTE PAIN AND BUPRENORPHINE

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Buprenorphine and Acute Pain

- Paucity of quality data
- Conflicting study results
- Consensus recommendations from APS, ASRA, ASA
  - –Appropriate pre-operative planning for analgesia
  - –Perioperative education
  - –Use of a validated assessment tool
  - –Multimodal analgesia
    - •Pharmacologic, non-pharmacologic, physical modalities (TENS)
    - •Oral therapy ASAP after surgery
    - •Local infiltrated anesthetics

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Challenges of Pain Management With Buprenorphine

- Post-op pain control difficult whether therapy is continued or stopped
- Possible inhibition of traditional opioids analgesia response
  - –High receptor binding affinity
  - –Slow dissociation rate from receptor
  - –Long half-life
  - –Partial agonist properties can inhibit the analgesia of traditional opioids
- High pure mu opioid dose needed to overcome the strong receptor affinity
- Difficult for naloxone to reverse
- Relapse may be a consequence of stopping BUP to treat the acute pain

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Considerations for Pain Management

- *Mu* receptors may be available in low dose buprenorphine therapy
- Treatment options differ based on clinical situation
  - –Chronic pain vs. substance use disorder vs. combination
  - –Elective vs. emergent procedures
  - –Anticipated pain severity
- Regional analgesia use may minimize opioid requirements
- Be aware of unreported use of BUP for self treatment of SUD
  - –Patient may not respond to usual doses
  - –Overdose risk increases after 48-72 hours

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Scenario 1

- HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, and has been successfully managed on Bup/NALx 16 mg/4 mg for 5 years.
- The Team wants recommendations on how to treat her pain post-operatively as well as what to do about the BUP/NALx?

- ***What are some ways that HW's pain can be managed post-op?***
- ***Does the use of BUP for substance use disorder change how you may manage the patient?***

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Best Practices for the Management of Acute Pain with Buprenorphine Maintenance Therapy

Figure 17: Suggested clinical algorithm for acute pain in patients receiving opioid agonist therapy who require analgesics[37]

Best practices	Methadone users	Buprenorphine users*
Confirm or verify the patient's methadone or buprenorphine dose	Continue maintenance dose	Continue buprenorphine and titrate short acting opioid
Inform the program or prescribing physician	Use short acting opioids	OR Divide buprenorphine dose to every 6-8 hours
Ensure access to naloxone	Dose may need to be higher or more frequent than usual	OR Discontinue buprenorphine and use opioid analgesics, convert back when acute pain has subsided

*Treatment should be chosen based on anticipated duration of pain, treatment setting, and treatment response

Managing Acute Pain in the Elderly. https://alosahealth.org/clinical-modules/pain/. accessed 9/11/2019

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Best Practices for the Management of Acute Pain with Buprenorphine Maintenance Therapy

- Current recommendation is to continue Bup/NalX unless extenuating circumstances
- For all patients, rely on multi-modal analgesia and nonopioids as a backbone as able/tolerated
- Ensure communication with outpatient BUP/NalX provider and support services

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Options for Acute Pain Management with BUP/NALx Therapy

1. Continue home regimen daily or in divided doses (3-4 times a day)
   - –use additional BUP/NALx as needed (PRN) for breakthrough pain
     OR
   - –Use traditional short-acting opioids PRN
   - –Consider lowering BUP dose to <16 mg
2. Discontinue BUP/NALx and convert to a traditional opioid
   - –Resume maintenance dose after acute pain subsides
   - –Caution if substituting methadone
3. Lower dose to < 16 mg daily, use traditional short-acting opioids PRN

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Option 1: Buprenorphine/naloxone PRN for Acute Pain

Will it work?

- High dose BUP/NALx* historically associated with a ceiling effect
  - – Questionable efficacy with additional BUP for acute pain in patients on MAT?
- Case study showed BUP/NALx dosing PRN was an effective option for short term analgesia in the setting of SUD
- May be an option where high risk of relapse exists
  - –More studies needed
- Buprenorphine IV in NPO patients?
  - –Being used more at this time due to IV opioid shortages

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*buprenorphine can be substituted in a supervised setting based on availability and cost

Option 1: BUP/NALx *PRN for HG*

HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, but is successfully managed on BUP/NALx 16mg/4mg daily for 5 years

- Current dosing can be continued or divided 3-4 times a day
  - HG currently takes BUP/NALx 16mg/4mg once daily
    - Baseline dose will not treat additional acute pain
    - BUP/NALx 4 mg/1 mg sublingual (SL) every 6 hours ATC
  - Breakthrough pain dosing initiated at 2mg/0.5 mg1-2 SL q4h PRN
  - *HG used a total of 32 mg BUP/NALx per day through post op day 2*
  - *As acute pain subsided, dose was de-escalated over the next 10-14 days without loss of analgesia*

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Option 2: Converting to Traditional Opioid Therapy

- May be preferred in very stable patients or for extensive pain with severe anticipated pain, although experts are now advocating to continue BUP/NALx
- Stop BUP/NALx therapy prior to surgical procedure
  - 2-4 weeks prior to procedure is optimal; stop at a minimum of 5 days pre-op
- Bridge with short acting opioid during transition
  - High opioid doses may be needed due to tolerance
- Utilize short acting opioids PRN while BUP/NALx leaves the system
- Concerns in SUD patients
  - May re-initiate cravings and euphoria
  - Risk of relapse is a concern during the bridging period prior to surgery
  - Caution with use of methadone in bridging phase

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Option 2: Opioid therapy plan for HG

- ***HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, but is successfully managed on BUP/NALx 16mg/4mg daily for 5 years.***
- Stop buprenorphine at least 5 days prior to surgery
- Bridge HG with long acting/short acting opioids
  - If BUP used for pain, short acting opioids recommended
- Utilize a PCA with/without a continuous infusion
  - Choose an opioid with high affinity for mu receptor (hydromorphone, fentanyl)
  - Utilize higher opioid doses to compete with BUP at the mu receptor
- Monitor for signs/symptoms of intoxication or relapse, especially during bridging

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Restarting *BUP/NALx*

- Buprenorphine can be restarted once pain can be controlled with non opioid options
- Opioids should be stopped completely before restarting BUP/NALx
- When transitioning an opioid tolerant patient, stop opioids and restart BUP/NALx when symptoms of mild withdrawal are seen
- Reintroduction should be restarted per recommendations for induction
  - Generally based on (COWS>6-8)

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Scenario - 2

- ***HG was in a car accident and is admitted with a broken femur and a few broken ribs. She has a history of SUD but has been successfully managed with buprenorphine/naloxone for the past 5 years. She is requiring surgery for pinning the break.***
- ***The patient would like to continue BUP/NALx. When she had recent breast surgery, and BUP/NALx was stopped, she reported poor pain control and cravings for opioids.***
- **Will continuing BUP/NALx help or hinder pain control?**

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Option 3: Continuing BUP/NALx using Traditional Opioids PRN

- Stopping BUP/NALx can be very stressful for the patient
  - Encourage patients to take an active role in the treatment plan
  - Educate patients on time course and realistic goals of post-op treatments
- Fear of pain and use of traditional opioids in the peri-operative period can trigger a relapse
- ICU setting recommended due to the need for high opioid doses post op
- Recommend continuing BUP/NALx in the following scenarios
  - Procedures where co-analgesics and regional anesthesia would be effective
  - Procedures associated with mild post operative pain
  - Patients at high risk of relapse

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VA Evidence Review 2019

- Limited evidence to address with confidence any specific strategy on the management of acute pain in patients on MAT
- Three retrospective studies support:
  - –Continuing the use of MAT for patients undergoing major surgery may reduce overall opioid doses
  - –Patients on MAT are opioid-tolerant and need higher doses of opioid agonists for effective pain control
  - –Discontinuing MAT can lead to patient disengagement from care
- Only one case report supporting the need to discontinue BUP in order to control severe pain

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Veazie S,et al. Department of Veterans Affairs. VA ESP Project #09-199; 2019

Option 3: Continuing BUP/NALx *Peri-Operatively for HG*

- ***HG was in a car accident and is admitted with a broken femur and a few broken ribs. She has a history of SUD but has been successfully managed with buprenorphine/naloxone for the past 5 years***

- HG will continue home dose of BUP throughout the post op period
- A TAP block will be used intra-operatively to help minimize opioids post operatively
- Fentanyl PCA was started at 50 mcg q6 min patient demand with no continuous
- Acetaminophen 1 g PO every 8 hours; ketorolac 15 mg IV q6h for first 48 hours
- Ketamine/dexmedetomidine will be considered if the pain is refractory

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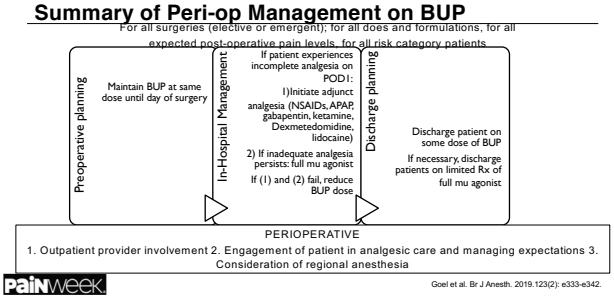
Efficacy Evidence continuing *BUP/NALx* Perioperatively

Type of Study	Methods	Results
Case series with 5 patients (2010)	Retrospective review of patients undergoing major surgery maintained on stable sl *BUP/NALx* doses (2-24 mg/day)	Post op pain controlled with oral/IV full agonists
Observational study with 8 patients (2009)	Review of peri-partum acute pain management in buprenorphine maintained patients	Response seen when additional opioids used for pain
Double blind RCT (2009)	Comparing PCA with buprenorphine alone, morphine alone, and in combination	Buprenorphine did not affect analgesia from morphine
Retrospective cohort (2010)	Comparison of BUP maintained patients with matched controls	BUP patients experienced more post-partum pain requiring 47% more opioids
Sub-analysis of MOTHER study (2011)	Looking at differences in pain management during delivery and for 3 days post-partum	No differences seen
Retrospective cohort (2013)	Looking at 11 BUP patients post operatively in conjunction with PCA	No significant differences in PCA requirements, pain scores, N/V, sedation

Summary of Peri-op Management on BUP



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Goel et al. Br J Anesth. 2019.123(2): e333-e342.

What Is Needed?

- Future research
  - Well-described studies examining specific acute pain management strategies and its effect on patient outcomes
  - Assessment of the efficacy of nonopioids and adjuvants in patients on MAT to control acute pain
  - Assessment of the benefits and harms of adjusting the dose and/or dosing schedule of MAT
  - To evaluate effective acute pain management in patients with OUD on naltrexone
  - Measurement of patient outcomes

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Veazie S,et al. Department of Veterans Affairs. VA ESP Project #09-199; 2019

Buprenorphine and Use in Pregnancy

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Scenario 3

- HG has remained cancer free, and remains maintained on her dose of BUP/NALx. Her biological clock is ticking; she is happy to report that she is now pregnant. She is concerned that he BUP/NALx will be harmful for her baby.
- ***How can we provide safe and adequate pain control during delivery and post partum periods in a patient maintained on BUP or BUP/NALx?***

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Substance Use Disorder in Pregnancy

Substance use during and following pregnancy often lead to medical issues in the fetus, in addition to mom → Maternal and/or fetal acquisition of sexually transmitted infections often co-exist with risky behaviors → Up to 80% SUD pregnancies are unplanned compared to 50% of unplanned pregnancies in the general population → Other issues common in pregnant patients with SUD
- Psychiatric illness
- Poor adherence to prenatal care
- Poor eating habits
- Post-partum depression

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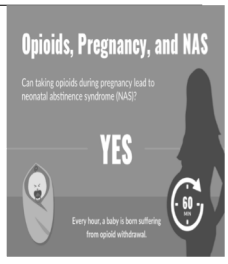
When Substance Use Disorder Exists

- MAT is recommended over withdrawal management
  - –Withdrawal symptoms may lead to relapse
- Women currently on MAT should continue treatment
  - –Usual dose is the patient's baseline analgesia
  - –Additional analgesia may be needed peri-partum
- Medically supervised withdrawal not recommended due to possible fetal compromise & high relapse/overdose risk
- Neonatal abstinence syndrome is a risk in women with substance use disorder



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Treatment of the Pregnant User

Pregnant women often motivated to change bad behaviors

Screen pregnant women for OUD at first visit and regularly thereafter

Pregnant substance users may be treated in a hospital beyond the 72 hour rule

Opioid agonist treatment is standard of care

Buprenorphine	Methadone

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Buprenorphine and Pregnancy

- Opioid use in pregnancy can be considered a health emergency due to possible deleterious effects on the fetus
- Three randomized controlled trials looked at different outcomes in BUP maintained pregnant women
  - Maternal efficacy, fetal effects, neonatal effects, effects on breast milk, developmental effects
- Additional 44 non-randomized studies also reviewed
  - 28 involved individual samples

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Study Highlights

- Retention rates similar in buprenorphine and methadone patients in MOTHER trial
- Dose increases of both methadone and buprenorphine may be needed
- Patients on MAT are at risk for increased pain during delivery and post partum
- Buprenorphine has no greater, and possibly minimal risk to the fetus compared to methadone
  - Less suppression of fetal heart rate
  - Intrauterine growth restriction seen, but frequency compared to methadone unknown
- Neonatal abstinence syndrome incidence similar between BUP and methadone
  - Approximately 50% incidence
  - Conflicting LOS data between randomized and non-randomized studies

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Buprenorphine Pearls

- Distinguishing use for management of pain from using for SUD is important when developing an acute pain plan
- Hydromorphone or fentanyl are the best choices for acute pain management if patient is receiving buprenorphine
- Utilizing co-analgesic agents is key in providing pain control
- When BUP stopped emergently, consider monitoring patient in a controlled setting for 3 days after discontinuation
  - Initial high dose opioids needed for pain control can cause overdose when BUP is out of the system
- MAT is preferred over withdrawal therapy in current SUD setting

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Take home points

- Multimodal analgesia should be used when possible to minimize opioid use
- Practitioners must anticipate the need for large doses of traditional opioids and detailed preoperative discussion with patients
- Close monitoring is needed when opioids are used in conjunction with buprenorphine
- Evidence based guidelines for the acute pain and perioperative management for patients on chronic buprenorphine is needed.
- Evaluation of SUD and treatment in the pregnant patient needed
- Additional research needs to be conducted to determine the best perioperative regimen for acute pain management in this population

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Questions??

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