



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

Tanya J. Uritsky, PharmD, BCPS, CPE

Disclosure

- Nothing to disclose



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.



Scenario 1

- HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, but is managed on buprenorphine/naloxone (BUP/NALx) and has been clean 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?



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 the BUP/NALx will be harmful for her baby.
- How do we manage her pain during and after delivery?

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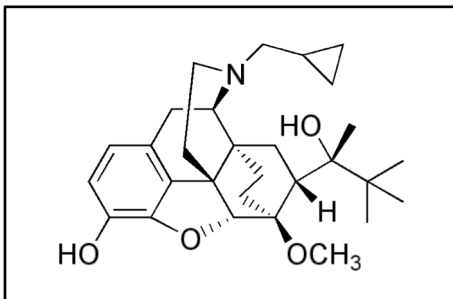
Buprenorphine Pharmacology

Tanya Uritsky, PharmD, BCPS, CPE

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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; inverse agonist - kappa receptor
- Has high affinity and binding capacity for the mu receptor, but low intrinsic activity
- $T_{1/2}$ = 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

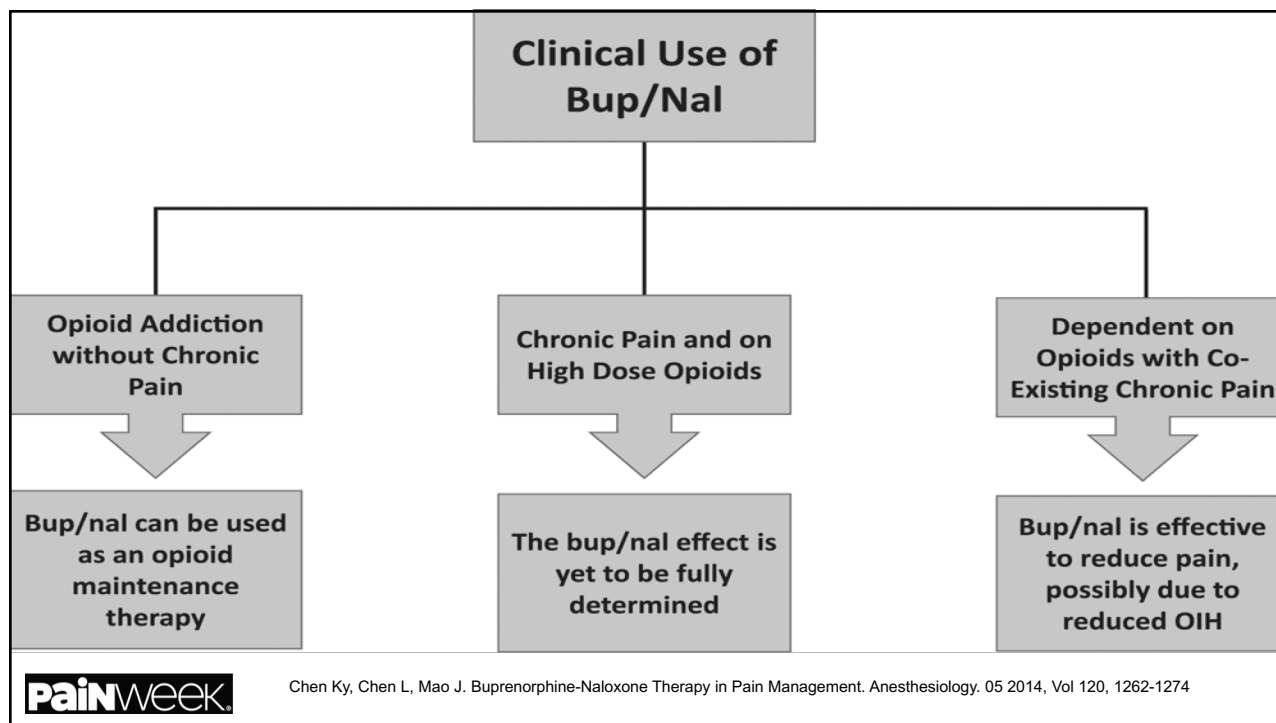
- Potent analgesic – can produce effective analgesia with only 5-10% of mu receptors occupied
- Even though buprenorphine has a short half-life (IV), it has a long duration of action.
- Besides half-life, the duration of action of a substance is also determined by receptor affinity, meaning the strength with which a substance binds to a receptor.
- Buprenorphine has a very high affinity for opioid receptors, and it will continue to occupy the 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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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

Dosing for Pain

▪ SL

- 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”, mid-level can 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

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

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Dosing

▪ Topical: Patch

- Titration Interval: min = 72 hours; q 7 days
- Opioid-naïve patients
 - Initial: 5mcg/hour applied q 7 days
- Non Opioid-naïve - patients receiving:
 - Max. dose= 20 mcg/hour applied q 7 days
 - May not provide adequate analgesia & consider use of alternate analgesic
 - ↑ Risk of QTc prolongation w/ doses \geq 20 mcg/hour
 - 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
 - Saquinavir
- Benzodiazepines
- Fluvoxamine
- Ketoconazole

Decreased opioid effect

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin

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ACUTE PAIN AND BUPRENORPHINE



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



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 when treating acute pain in patients with SUD



Considerations for Pain Management

- Formulation and dosing
 - 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
 - Pain severity
- Regional analgesia use may minimize opioid requirements
- Be aware of illegal use of BUP for self treatment of SUD
 - Patient may not respond to usual doses
 - Overdose risk increases after 48-72 hours



Scenario 1

- HG is going to be admitted for scheduled mastectomy. She has a history of opioid addiction, but is managed on BUP/NALx 16mg/4mg daily and has been clean 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?*



Acute Pain Management with Buprenorphine/Naloxone Therapy

Alternatives for the treatment of acute and post-operative pain in the setting of chronic BUP/NALx therapy

- Continue home regimen daily or in divided doses (3-4 times a day)
 - use additional BUP/NALx as needed (PRN) for breakthrough pain
- Convert to a traditional opioid
 - Resume maintenance dose after acute pain subsides
 - Caution if substituting methadone
- Continue home regimen and use traditional short acting opioids PRN additional pain control



Option 1: Buprenorphine/naloxone PRN for Acute Pain

Will it work?

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



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

Option 1: BUP/NALx PRN for HG

- Current dosing can be continued or divided three to four times a day
 - HG currently takes BUP/NALx 16mg/4mg once daily
 - Baseline dose will not treat additional acute pain
- Dose was increased by 1/3 over baseline for additional anticipated severe pain from procedure
 - BUP/NALx 8 mg/2 mg sublingual (SL) every 8 hours SCH
 - Breakthrough pain dosing initiated at 2mg/0.5 mg 1-2 SL every four hours PRN moderate to severe pain
 - *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*



Option 2: Converting to Traditional Opioid Therapy

- Good option for elective surgery
- 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



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 managed on BUP/NALx 16mg/4mg daily and has been clean 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



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?**



Option 3: Continuing BUP/NALx using Traditional Opioids PRN

- In SUD patients, 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
- Minimal data available
- May consider 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



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

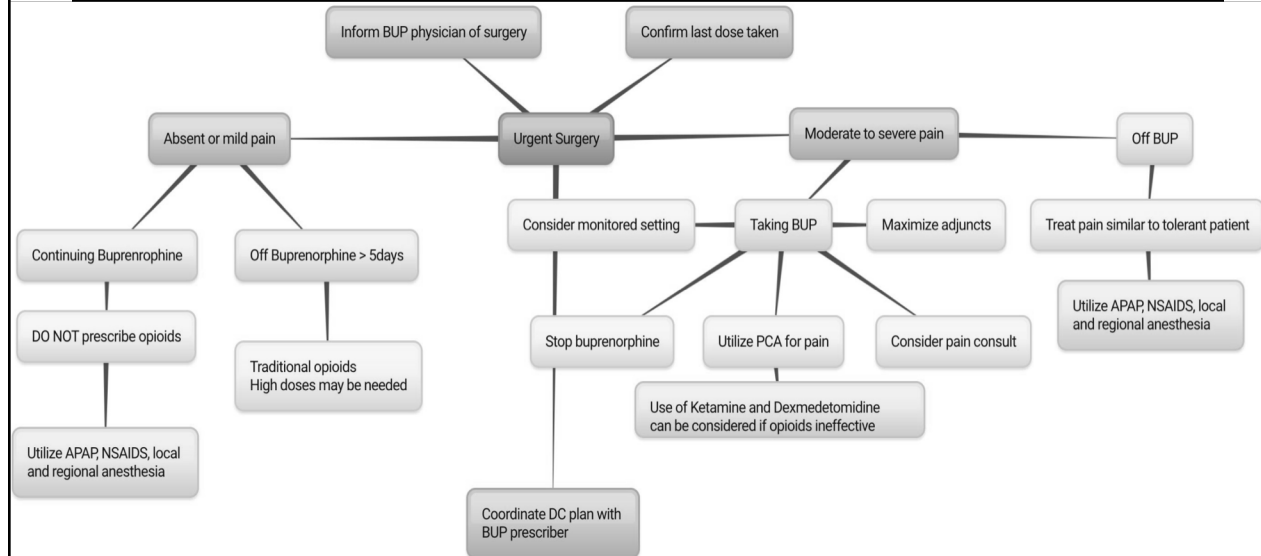
- ***HG was in a car accident and is admitted with a broken femur and a few broken ribs. She has a history of SUD but has been successfully managed with buprenorphine/naloxone for the past 5 years***
- HG will continue home dose of BUP throughout the post op period
- A TAP block will be used intra-operatively to help minimize opioids post operatively
- For acute pain, a fentanyl PCA was started at 50 mcg q6 min patient demand with no continuous
- Acetaminophen 1 g every 8 hours added
- Ketamine/dexmedetomidine will be considered if the pain remains severe despite the current therapies



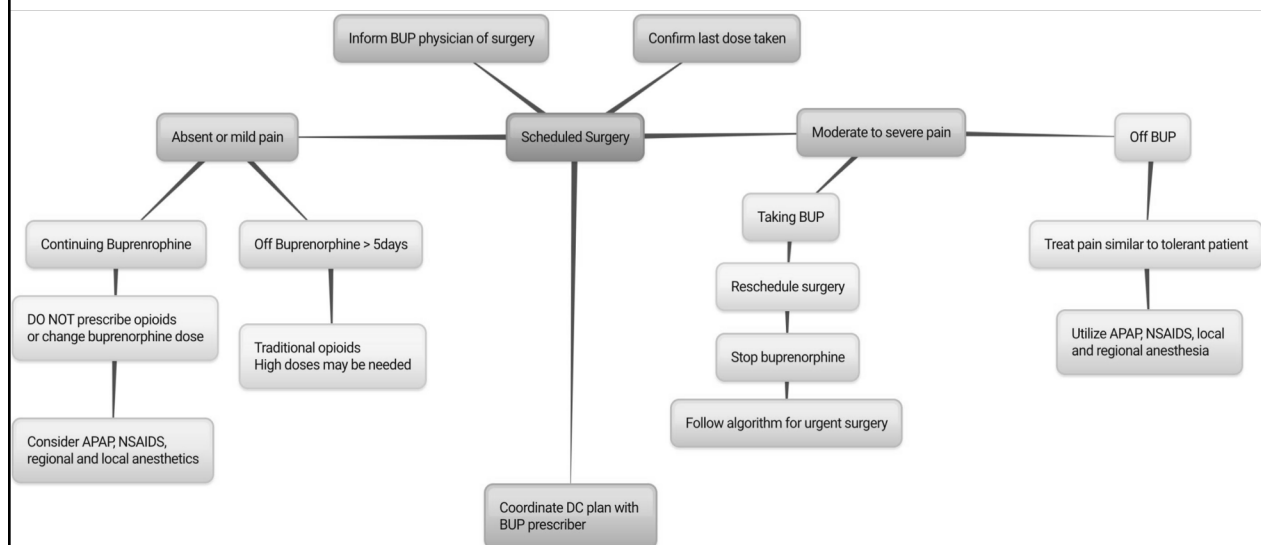
Efficacy Evidence continuing *BUP/NALx* Perioperatively

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

Emergent Acute Pain Algorithm



Scheduled Acute Pain (Surgery) Algorithm



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



Buprenorphine and Use in Pregnancy

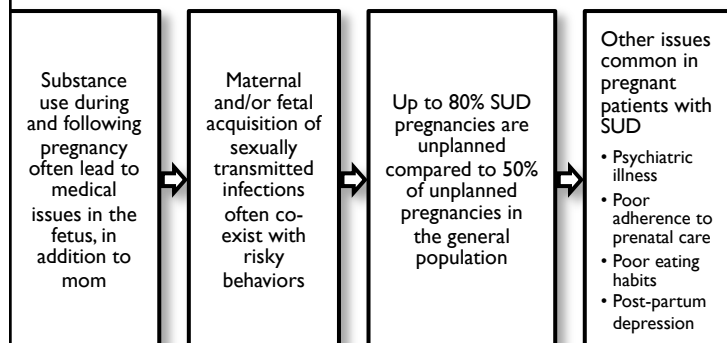


Scenario 3

- 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 the 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

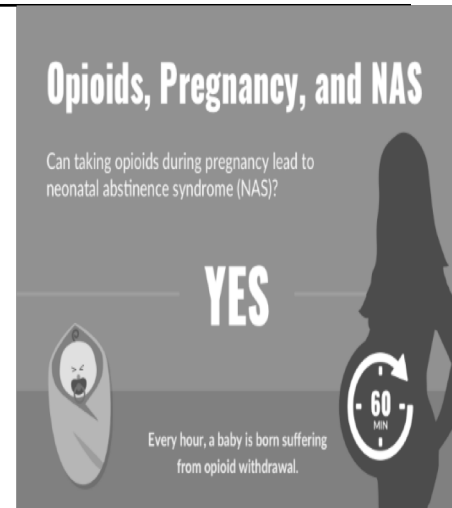


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When Substance Use Disorder Exists

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

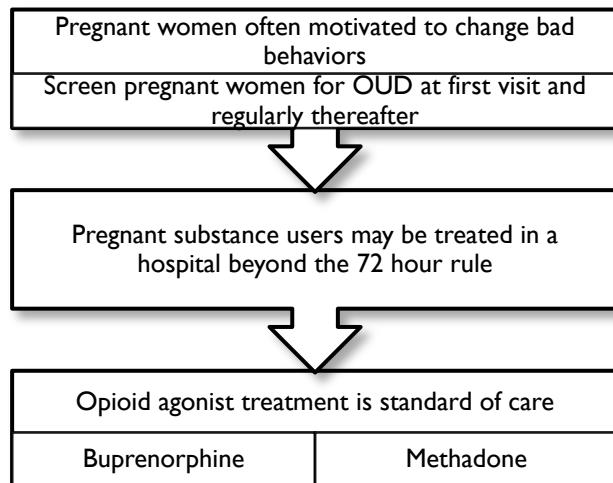
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Treatment of the Pregnant User



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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



Study Highlights

- Retention rates were similar in both the buprenorphine and methadone patients in the MOTHER trial
- Dose increases of both methadone and buprenorphine may be needed during pregnancy to maintain therapeutic blood levels
- Patients on MAT are at risk for increased pain during delivery and during the post partum phase
 - additional pain medications will be required to treat peri- and post-delivery pain
- 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 in both groups
 - Conflicting LOS data between randomized and non-randomized studies



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 in BUP maintained patients, especially in the setting of substance abuse
- When BUP stopped emergently, consider monitoring patient in a controlled setting for 3 days after discontinuation
 - Initial high doses needed for pain control can cause overdose when BUP is out of the system
- MAT is preferred over withdrawal therapy in current SUD setting



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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